National Library of Canada
Canadian Theses Service
Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada
Service des thèses canadiennes

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, tests publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30.

NL-339 (r. 88/04)

Canada

THE UNIVERSITY OF ALBERTA

IN SITU LESIONS AND INVASIVE LOBULAR CARCINOMA OF THE FEMALE BREAST: A DETAILED CLINICOPATHOLOGICAL ANALYSIS OF CASES AT THE UNIVERSITY OF ALBERTA HOSPITAL FROM 1955 TO 1985 .

BY

William John Orrom

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

SPRING 1988

Permission has been granted to the National Library of Canada to microfilm this thesis and to lend or sell copies of the film.

The author (copyright owner) has reserved other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without his/her written permission.

L'autorisation a été accordée à la Bibliothèque nationale du Canada de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur (titulaire du droit d'auteur) se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation écrite.

ISBN 0-315-42739-6

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: William John Orrom

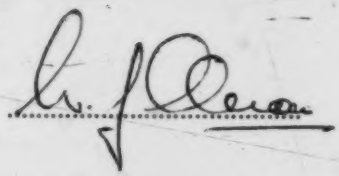
TITLE OF THESIS: In Situ Lesions and Invasive Lobular Carcinoma of the Female Breast: A Detailed Clinicopathological Analysis of Cases at the University of Alberta Hospital from 1955 to 1985.

DEGREE FOR WHICH THIS THESIS WAS PRESENTED: MASTER OF SCIENCE

YEAR THIS DEGREE WAS GRANTED: Spring 1988

Permission is hereby granted to the UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.



10444 70 Ave.,
Edmonton, Alberta.
Canada. T6H 2E8

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read and recommend to the Faculty of Graduate Studies and Research, a thesis entitled In Situ Lesions and Invasive Lobular Carcinoma of the Female Breast: A Detailed Clinicopathological Analysis of Cases at the University of Alberta Hospital from 1955 to 1985. Submitted by William John Orrom in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE IN EXPERIMENTAL SURGERY.

Alun G. Thurston
(Supervisor)

August 6 1987

TO MY WIFE, IRENE
AND MY PARENTS.

ABSTRACT

1,025 cases of surgical breast pathology with all diagnoses except those clearly identified as invasive duct cancers and non-proliferative benign breast biopsies were reviewed from 1955 to 1985. From this review, 76 cases of duct carcinoma in situ (DCIS), 21 cases of lobular carcinoma in situ (LCIS), 136 cases of invasive lobular carcinoma (I.L.C.) and 19 cases of invasive duct carcinoma with associated LCIS (I.D.C. + LCIS) were identified. Clinical follow-up was obtained at the Cross Cancer Institute in Edmonton, Alberta.

5% of all cancers were in situ lesions, 78% ductal and 22% lobular. Most of these patients presented with a mass. The mean age at presentation for LCIS was 48 years, significantly lower than DCIS (57 years). A higher proportion of patients with LCIS were premenopausal and more of the patients gave a family history of breast cancer (75% versus 33%). Bilaterality was high in both lesions (24% in DCIS and 57% in LCIS). In those with DCIS, family history was identified as a risk factor for bilaterality.

Of 14 patients with DCIS treated without mastectomy, 6 developed ipsilateral invasive cancers (43%). All were of the ductal variety. Of 13 patients with LCIS, 4 developed subsequent invasive cancers, 2 ipsilateral and 2 contralateral. No risk factors for the development of invasive cancer could be identified in either group.

9% of all cancers of the female breast in this series were invasive lobular. Patients with I.L.C. showed a high incidence of bilaterality (20%). This was increased in the presence of LCIS. Patients with larger tumours had an increased risk of developing a second primary breast cancer. In those patients with I.L.C. and associated LCIS, a younger age at diagnosis, an increased proportion of premenopausal patients and lower mean hormone receptor levels (estrogen and progesterone) were seen when compared with patients with

invasive duct cancers at the Cross Cancer Institute from 1971 to 1985. Patients with I.L.C. had an improved actuarial survival over 12 years when compared with invasive duct cancers. The type of surgical treatment did not influence survival.

In conclusion, both LCIS and DCIS carry significant risks of developing bilateral disease and of developing invasive cancers. Close follow-up is mandatory with both of these lesions. Invasive lobular carcinoma carries a significant risk of bilaterality and, in spite of lower mean hormone receptor levels, shows an improved actuarial survival when compared with invasive duct cancers.

ACKNOWLEDGEMENTS

The author wishes to thank the following for their contributions to the production of this research work:

Dr. Bruce Mielke for his many in hours in the review of the histological material, his suggestions, teaching and supervision.

Dr. Olin G. Thurston for his very valuable suggestions and supervision.

The Breast Unit at the Cross Cancer Institute for their great support and help. In particular Mrs. Carol May for all the patient data and Mrs. Heather Jenkins for her superb work in accessing the computer information files and developing the survival curves.

TABLE OF CONTENTS

	Page
I. INTRODUCTION, OBJECTIVES AND LITERATURE REVIEW	1
Introduction and Objectives	1
In Situ Carcinoma	2
Lobular Carcinoma In Situ	3
Duct Carcinoma In Situ	8
Invasive Lobular Carcinoma	11
II. METHODS AND RESULTS	17
Duct Carcinoma In Situ	18
Lobular Carcinoma In Situ	21
Invasive Lobular Carcinoma	22
III. DISCUSSION AND CONCLUSIONS	27
IV. TABLES	32
V. FIGURES	54
VI. BIBLIOGRAPHY	73

LIST OF TABLES

Table		Page
I	Risk of Invasive Cancer Following LCIS	32
II	Methods Proposed in the Treatment of LCIS	33
III	Risk of Invasive Cancer Following Intraductal Carcinoma Treated by Biopsy Only	34
IV	Summary of Selected Series of Invasive Lobular Carcinoma	35
V	Results of Histological Review for DCIS	36
VI	Clinical Data - Duct Carcinoma In Situ	37
VII	Method of Treatment DCIS	38
VIII	Comparison of patients with DCIS developing subsequent invasive carcinoma with those who did not	39
IX	Histological Types of Bilateral Breast Cancers in Patients with DCIS	40
X	Comparison of patients with DCIS developing bilateral breast carcinomas with those who did not	41
XI	Bilateral Cancers in Patients with LCIS- Histological Types	42
XII	Comparison of patients with LCIS with those with DCIS	43
XIII	Comparison of patients with LCIS developing subsequent invasive carcinoma with those who did not	44
XIV	Clinical Data Invasive Lobular Carcinoma Compared with Invasive Duct Carcinoma	45
XV	Clinical Data Invasive Lobular Carcinoma with Associated LCIS Compared with Invasive Duct Carcinoma	46
XVI	Clinical Data Invasive Lobular Carcinoma without Associated LCIS Compared with Invasive Duct Carcinoma	47

LIST OF TABLES (CONTINUED)

Table		Page
XVII	Clinical Data Invasive Lobular Carcinoma with Associated Invasive Duct CarcinomaCompared with Invasive Duct Carcinoma Alone	48
XVIII	Clinical Data Invasive Duct Carcinoma with Associated LCIS Compared with Invasive Duct Carcinoma Alone	49
XIX	Clinical Data Invasive Lobular Carcinoma with Associated LCIS Compared with Invasive Lobular Carcinoma Alone	50
XX	Clinical Data Invasive Lobular Carcinoma. Patients with bilateral disease compared with those with unilateral disease only.	51
XXI	Bilateral Cancers Associated with Invasive Lobular Carcinoma	52
XXII	The Treatment of Invasive Lobular Carcinoma	53

LIST OF FIGURES

Figure		Page
1	Histological Diagnosis of Cases Prior to Review	54
2	Results of Histological Review	55
3	Treatment of DCIS by Decade	56
4	Actuarial Survival DCIS: Purely In Situ Lesions vs. Microinvasive Lesions	57
5	Actuarial Survival DCIS with Primary Radiotherapy (1° RT) vs. DCIS Without Primary Radiotherapy	58
6	Actuarial Survival DCIS: Breast Conservation vs. Mastectomy	59
7	Actuarial Survival LCIS vs. DCIS	60
8	The Treatment of Invasive Lobular Carcinoma by Decade	61
9	Actuarial Survival I.L.C. vs. I.D.C. by year	62
10	Actuarial Survival I.L.C. with associated LCIS vs. I.D.C.	63
11	Actuarial Survival I.L.C. without associated LCIS vs. I.D.C.	64
12	Actuarial Survival I.L.C. with associated I.D.C. vs. I.D.C. alone	65
13	Actuarial Survival I.D.C. with associated LCIS vs. I.D.C. without associated LCIS	66
14	Actuarial Survival I.L.C. by Menopausal Status	67
15	Invasive Lobular Carcinoma: Actuarial Survival according to lymph node status	68

LIST OF FIGURES (CONTINUED)

Figure		Page
16	Actuarial Survival I.L.C. by Stage at Presentation	69
17	Actuarial Survival I.L.C. by Size of Primary at Presentation	70
18	Actuarial Survival I.L.C. by Year at Diagnosis	71
19	Actuarial Survival I.L.C. by Method of Surgical Treatment.	72

Introduction

The treatment of primary breast cancer is a controversial issue ranging from radiation only, "lumpectomy", segmental resection with and without radiation , the many variations of mastectomy including modified radical, "simple" and "total" mastectomy with and without radiation, to the classic Halsted radical mastectomy, which is rarely employed today. As less radical procedures for both invasive and in situ breast cancers become more popular it will be important to identify, if possible, any clinical, epidemiological, or histopathological factors to choose appropriate therapy for the individual patient. Hopefully, it may become possible to identify those patients who would benefit from more radical procedures from those who would be adequately treated with more conservative procedures. In this vein, *in situ* lesions might be reassessed from the standpoint of their natural history, the incidence of subsequent invasive cancer in those treated with breast conserving procedures and the risk of cancer in the opposite breast. Identifying those at risk of developing invasive cancer or bilateral breast cancers would define a subset of patients better treated with a more radical surgical approach. Also of importance in the management of patients with breast cancer is the histological type. In situ lobular carcinomas have a higher incidence of bilaterality with a lower or similar risk of subsequent invasive carcinoma when compared with in situ duct carcinoma[46]. With regard to invasive cancers, those showing infiltration of dermal lymphatics ("inflammatory carcinoma") have a grave prognosis[46]. As well, signet ring carcinomas appear to have a poorer prognosis than the more common invasive duct carcinoma[46]. Invasive papillary carcinomas, medullary carcinomas, mucinous carcinomas and tubular carcinomas all appear to have a more favourable outlook[46]. Invasive lobular carcinomas have been reported to have both a better and a worse prognosis in

the literature when compared with invasive duct cancers[46]. Bilaterality has been shown to be increased in those patients with invasive lobular carcinomas[46].

With many of the above considerations in mind, a review of *in situ* carcinomas and invasive lobular carcinomas of the breast was carried out with the hope of further delineating the following:

A. *IN SITU* CARCINOMAS

1. The incidence of *in situ* lesions.
2. The risk of subsequent invasive cancer in patients treated with breast conserving surgery.
3. The identification of any clinical, epidemiological, or histopathological features identifying those at greater risk of developing subsequent invasive carcinoma.
4. The risk of carcinoma in the opposite breast and risk factors for the development of bilateral disease.

B. INVASIVE LOBULAR CARCINOMA

1. The incidence of invasive lobular carcinoma
2. The prognosis in comparison to invasive duct carcinoma.
3. The incidence of bilaterality.
4. The identification of any clinical, epidemiological, or histopathological features identifying those at greater risk of developing bilateral disease.

In Situ Carcinoma

In 1932, Broders introduced the term "carcinoma *in situ* " to describe " a condition in which malignant epithelial cells and their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformation. At least they have not migrated beyond the juncture

of the epithelium and the so-called basement membrane."[1] *In situ* carcinomas of the breast comprise 1.9-5.3% of all carcinomas of the female breast, of these 20-37% are *in situ* lobular carcinomas and 60-80% are *in situ* ductal lesions[2,3,4]. These lesions are becoming increasingly important as the improvements in mammography detect more and more carcinomas of the breast at this early stage. In the past, detection of *in situ* carcinomas of the breast, particularly those of lobular origin, was more or less a serendipitous finding in surgical biopsies performed for other clinically apparent lesions. In the nationwide Breast Cancer Demonstration and Detection Project (BCDDP), 25% of all cancers detected at the first screening were *in situ* carcinomas, underlining the increasing importance of these lesions[5].

Lobular Carcinoma In Situ

This lesion was first described in 1941 by Foote and Stewart[6] and independently by Muir[7]. It is characterized microscopically by variably distended lobules filled with closely packed monotonous cells obliterating the luminal space and having few mitotic figures. There are two morphological subtypes designated type A and B by Haagensen[8] . The distinctions can be made on the basis of nuclear size and chromatin content, amount and staining reactions of the cytoplasm, number of mitotic figures, the presence or absence of necrosis, the pattern of growth, and the shape of the lobules. These distinctions do not appear to carry any prognostic significance. Retrograde involvement of ducts is not unusual. The tumour cells may squeeze between the cuboidal lining cells and the myoepithelial cells in a process termed "Pagetoid Spread"[9] This may be the predominant expression of the disease[8]. It is important to distinguish this from ductal carcinoma in situ that has spread down into the lobules, a process called "lobular cancerization". A cribriform

pattern, a more pleomorphic cell population, and cell necrosis indicate a ductal origin to the cells, with lobular cancerization[9]. LCIS is missed at frozen section examination of the tissue in two-thirds of cases requiring permanent paraffin sections for diagnosis in the majority of cases[10]. LCIS is therefore a common cause of false negative frozen section diagnosis[11].

Lobular carcinoma *in situ* (LCIS) tends to occur in a younger age group, usually premenopausal or perimenopausal women with an average age between 44- 46[8,12,16]. This is the reverse of the situation seen in patients with infiltrating breast cancers[17]. This predeliction for premenopausal females has suggested an hormonal role in the genesis of these lesions[8,18]. In an interesting study by Alpers and Wellings[18], breasts from random autopsies, cancer containing breasts, and those contralateral to cancer containing breasts were examined meticulously using a subgross technique. They found the incidence of LCIS to be very low in postmenopausal breasts. In breasts from random autopsies, LCIS was not seen and in breasts of women with breast cancer, the incidence was less than 14%. However, it must be pointed out that the detection of LCIS in post-menopausal females in the absence of exogenous hormone therapy is by no means rare[19].

The lesion is frequently bilateral[20,21] (20-50%) and multicentric (40-80% of cases)[6,18,20-23]. In spite of this high incidence of multicentricity, the incidence of multicentric invasive cancer is less than 5%[10]. With regard to the location of the lesion within the breast, Lambird and Shelley[22] have shown that the majority of LCIS is concentrated in the subareolar and periareolar upper-quadrant tissue. 50% of lesions were found within 5cm of the nipple in their study. The number of lobules involved in the biopsy is variable and does not influence the risk of subsequent invasive cancer or predict its multicentricity[12,17,24].

Rosen et al[10] report a 1% incidence of axillary node metastasis in the absence of invasion following extensive sectioning of the mastectomy specimen. Sunshine et al[16] also describe a patient who developed systemic metastases with no evidence of lymph node involvement following bilateral mastectomy for LCIS and again, no evidence of invasion in the primary lesion. Finally, Farrow reported 3 patients with purely *in situ* lobular carcinoma with metastases in a single ipsilateral lymph node[44].

LCIS very rarely presents as a palpable tumour but is usually diagnosed histologically in biopsies of other breast lesions, usually fibrocystic disease. There are no distinctive mammographic findings for LCIS, however fine-stippled calcifications are seen in 50% of cases, usually in the surrounding breast tissue, but occasionally in the focus of *in situ* carcinoma itself[25]. Since similar calcifications occur in a variety of benign breast diseases as well, they fail to provide sufficient specificity for making a diagnosis[26]. Ashikari et al reported a 57% incidence of positive or suspicious preoperative mammograms in patients with LCIS[23].

LCIS has generally been regarded as a precurser of invasive carcinoma and has been treated in most circumstances with ipsilateral mastectomy. There are several studies dealing with the problem of subsequent invasive carcinoma in patients with LCIS treated with biopsy only and these are summarized in table I. A wide variation in the subsequent incidence of invasive carcinoma can be noted, with a low of 13% in the series of Wheeler and Enterline[14], to a high of 35% in the study of Hutter and Foote[27]. In the series of Wheeler et al[14], 25 patients with LCIS were treated with biopsy only and *only one patient* (4%) developed an ipsilateral invasive cancer with an average follow-up of 17.5 years. Of great importance is the almost equal incidence of subsequent invasive carcinoma in the contralateral breast, up to 14% in the series of Rosen

et al[12]. In the study by Wheeler et al[14] there was no statistically significant difference in the incidence of subsequent invasive cancer between the ipsilateral and contralateral side. This was confirmed in Andersen's study in 1977[13]. Up to this point, it has not been possible to identify any clinical, epidemiological or pathological features that could predict which patients are more at risk of developing subsequent invasive carcinoma[19,28]. The risk is slightly increased in patients with a family history of breast cancer and among nulliparous females[12]. However, both of these factors are known to increase the risk of breast cancer , regardless of associated LCIS. In patients with LCIS, the risk of subsequent invasive carcinoma has been shown to be increased 7-12 times above that of the general population[6,7,8]. In the 1967 study by McDivitt et al[34] 50 patients with LCIS treated with biopsy only were followed. The estimated risk for invasive carcinoma was 8% after 5 years, 15% at ten years, 27% at 15 years and 35% after 20 years. However, several studies subsequent to this early report have not substantiated such high cumulative risks[13,14]. In Haagensen's series, the overall increased risk of invasive cancer was 7.2 , but in those patients with a sister or mother with breast cancer as well as LCIS with accompanying gross cystic disease, the risk was increased to 14 times that of the general population[8]. The risk of death from breast cancer was increased 11 times above that of the general population in the series of Rosen et al[7]. Half of the deaths could be attributed to the ipsilateral breast and half to the contralateral breast. It is important to note however, that in the literature, overall only 5% of patients with LCIS have died of breast cancer over long periods of follow-up[13].

The interval to development of invasive cancer following a diagnosis of LCIS ranges from 1 to 31 years[8,12-15,27] Rosen's data[12] shows a biphasic distribution with an initial peak at 5-10 years, followed by a second peak at 15-

19 years. A shift of the second peak to 20-24 years is seen with those cancers developing in the contralateral breast.

The carcinomas that develop are more commonly of the invasive ductal type (60%)[12-14]. This has been interpreted by some authors to indicate that LCIS is not a preinvasive lesion but rather is a high-risk marker[18,29]. However, as pointed out by Rosen[12], the incidence of invasive lobular carcinoma in his series of patients was 36%, a figure well above the usual incidence of this type of breast cancer (5-10% of all breast cancers[30-33]). The disproportionate number of invasive lobular carcinomas does suggest a relationship between the noninvasive and invasive lesions. Newman[31] saw evidence of LCIS in 72 of 73 invasive lobular carcinomas and concluded that the *in situ* form was a precursor of the invasive form.

The risk of subsequent invasive cancer is the important determinant of the surgical management of this disease. Many different treatment recommendations have been advocated by different authors and are outlined in table II. Those that advocate ipsilateral mastectomy feel that the risk of subsequent cancer is too high to leave treatment at follow-up only. In addition, they note the 5% incidence of invasive carcinoma found in mastectomy specimens performed for LCIS[21] as well as the high incidence of multicentricity as indicators for a policy of mastectomy. Others argue that any treatment policy must be directed equally to the contralateral breast, since it is at equal risk of subsequent invasive cancer, selecting a policy of bilateral mastectomy[16,35]. On the other hand, while 20-25% of patients will develop invasive cancer, the majority of patients (75-80%) will not. This will leave a large number of patients subjected to ipsilateral or bilateral mastectomy who would never develop invasive disease regardless of treatment. With this in mind, some authors feel the risk of subsequent invasive cancer to be low enough to justify a program of

close follow-up[8,13,14,36]. Lobular carcinoma *in situ* in this situation may be looked upon as a high risk marker for possible future invasive carcinoma[18,29]. In an article by Powers et al[37], he states: "both breasts may be considered as a single organ with the presence of LCIS in one breast indicating a varying propensity for all the breast parenchyma". With this in mind, he feels close follow-up of both breasts is the preferred treatment.

The question of contralateral breast biopsy has been addressed by several authors in the setting of LCIS. When no further therapy is planned for the ipsilateral breast, biopsy of the contralateral breast is not indicated since the finding of further LCIS would not be acted upon even if present. In Urban's original series[36], 12 of 39 simultaneous contralateral biopsies (30%) were positive (1 infiltrating and 11 noninfiltrating). In a study by Rosen et al[21], 28 of 57 contralateral biopsies (49%) were positive (6 infiltrating and 22 noninfiltrating).

In summary, lobular carcinoma *in situ* is a multicentric, bilateral disease affecting younger, premenopausal females. Approximately 20 to 25% of patients with this type of *in situ* lesion will subsequently develop invasive cancer, with an equal risk to either breast. An average interval of fifteen years from the time of initial biopsy to the development of invasive cancer is observed and the subsequent invasive cancer is usually of the ductal variety. The management of this lesion is controversial ranging from close follow-up to bilateral mastectomy.

Duct Carcinoma In Situ

Duct carcinoma *in situ* is characterized histologically by the intraductal proliferation of cells with a solid, papillary, or cribriform pattern of growth. The individual malignant cells have nuclei of variable size and shape with

numerous mitotic figures. There is very little supporting connective tissue, and areas of central necrosis in the ducts are common. Calcium salts frequently are deposited in these necrotic areas and can be identified by mammography[46]. Axillary node metastases have been reported from 0[11,31] to 2%[38] of cases of "purely" intraductal carcinoma with a figure of approximately 1% as the most commonly quoted incidence[23,39]. This could be explained by tissue sampling error with areas of stromal invasion missed during tissue sectioning. These lesions present as a discrete mass or thickening in 50-70% of cases[23,38]. 50% of these masses are central and 25% present with associated Paget's disease of the nipple[38]. In Ashikari's series of 71 cases[23], 11 (16%) presented with a nipple discharge while in von Rueden's series[39], 21% presented with this finding. In this latter series from 1984, only 52% of mammograms were abnormal, while in Ashikari's 1977 paper, 74% of mammograms showed a group or cluster of calcifications[23]. Specimen radiography may be helpful to ensure the suspicious area is sampled at the time of surgery[39]. Ashikari states that based on mammographic calcifications, 25% of cases biopsied will be positive for carcinoma[23].

The average age of females presenting with intraductal carcinoma varies from 48-55 years[4,23,38,39,41,42], with the majority being closer to 55[4] years or over. The age distribution closely mirrors that of invasive carcinoma[38] in contradistinction to the pattern seen with *in situ* lobular carcinoma. The incidence of multicentricity varies from 30 to over 50%[23,39,43,18], but bilaterality is not particularly high, being in the range of 15% and is therefore not usually a problem clinically[20,23,29,39].

The subsequent development of invasive cancer following biopsy only is limited to a few studies and these results are summarized in table III. It can be seen from this limited data that between 20 to 50% of patients with duct

carcinoma *in situ* will develop invasive carcinoma an average of ten years after the initial biopsy. Of great importance clinically is the fact that these subsequent cancers develop almost exclusively in the ipsilateral breast and are nearly always of the invasive ductal type[41,42]. In the study by Page et al[41], the risk of invasive cancer was increased 11 times that of an age-matched population. 5 of the 7 invasive cancers that developed in this study were in *the same quandrant* as the original biopsy. This is nearly identical to the findings of Betsill et al[42], where 4 of 7 subsequent cancers developed in the same quandrant as the original biopsy. Alpers and Wellings[18] report separate foci of DCIS or "ALA 4" (a lesion many would regard as DCIS) within breasts with a clinically identified breast cancer in 64% of patients. In breasts contralateral to clinically identified breast carcinomas, 61% showed evidence of DCIS or ALA 4. Their data supports the theory that mammary neoplasia is a disease of breast tissue, not of one breast in particular. They hypothesize that not all lesions identified as carcinoma in situ have the same propensity to undergo further malignant transformation.

The most common treatment for ductal carcinoma *in situ* has been mastectomy, with or without an axillary node dissection, usually limited to level I nodes. While some have advocated bilateral mastectomy[16], this certainly is not a popular surgical approach. The controversy that has begun to arise in recent years is between a less radical breast-preserving procedure versus mastectomy. Certainly the fact that the vast majority of subsequent invasive cancers appear in the same quandrant as the original biopsy make quandrantectomy with or without axillary node dissection a logical procedure. It is of note that the American College of Surgeons National Breast Cancer Survey [4] of 1980 showed no difference in the number of treatment failures between those treated with mastectomy and those treated with a breast

preserving procedure. As pointed out by Wolmark[29], with the increasing acceptance of breast preserving procedures for invasive cancer[45] it may become difficult to justify mastectomy for its preinvasive counterpart. However it must be pointed out that this disease is multicentric, that 6% of breasts removed for intraductal carcinoma show foci of invasive cancer[10], and that the studies documenting the eventual outcome of patients treated by biopsy only suffer from very small sample sizes. It is possible that the propensity of the invasive counterpart of duct carcinoma *in situ* to appear in the same quadrant as the original biopsy would not be born out in a larger series of patients.

In summary, ductal carcinoma *in situ* is a lesion found mainly in perimenopausal or postmenopausal females presenting with either a mass or nipple changes or as an abnormality on mammographic screening examination. Up to 50% of these lesions will go on to invasive carcinoma if treated by biopsy only. The subsequent invasive cancers are of the ductal type and are usually localized to the same quandrant as the original biopsy. The risk of subsequent invasive cancer is similar to that in lobular carcinoma *in situ* with the important proviso that the subsequent cancers appear to be limited to the ipsilateral breast while those of LCIS are distributed equally between the ipsilateral and the contralateral breasts.

Invasive Lobular Carcinoma

Invasive lobular carcinoma of the breast was first described by Foote and Stewart[47] in 1946. Since that time several other investigators have singled out invasive lobular carcinoma for specific study. Both *in situ* and invasive lobular carcinoma have been shown in an elegant article by Wellings[48] to originate from the terminal ductal lobular unit. Indeed, all but a small fraction of breast cancers appear to originate from this structure, both those identified as having a

ductal origin and those of lobular origin. It therefore appears logical, as pointed out by Azzopardi[9] , that these subtypes should be thought of as referring to histological and cytological entities rather than to sites of origin of the individual tumours.

The histological definition of invasive lobular carcinoma (I.L.C.) of the breast is presently in a state of transition. The differentiation of I.L.C. from invasive duct carcinomas (I.D.C.) may present few problems but at times the differentiation can be quite challenging[9,49]. The "classical" type of I.L.C. usually gives the least trouble in classification, although difficulty arises when features of invasive lobular and ductal carcinoma are combined in one tumour. The features of classical I.L.C. include small cells with little cytological irregularity and uniform staining, strands of infiltrating cells ("indian filing") in trabeculae usually of one cell thickness in a dense, fibrous stroma and a "targetoid" pattern of invasive cells about normal duct structures[47,50,52].

Recently, there have been other variants of I.L.C. recognized including solid[51], alveolar[52], trabecular[52], tubulolobular[58] and those with mixed histology. Fechner[51] described the solid variant in 1975 as the dominant or exclusive form of the tumour in 6 of 26 cases of I.L.C. reviewed. Azzopardi could not find a case in his series that was the exclusive or even the dominant pattern of the tumour[52]. Van Boegaert never saw this as a pure type of tumour but found it as the dominant type in 3 of 22 cases (13.7%)[62]. There is a possibility that this variant may be related to carcinoid tumours of the breast[56]. The alveolar pattern described by Azzopardi is one in which a mimicry of LCIS is seen in an invasive tumour and is thought to represent an attempt by the invasive tumour to reproduce alveolar or "acinar" structures[52]. This pattern is not specific to I.L.C. as it occasionally is seen as a component of I.D.C.[52]. At the ultrastructural level, the tumour cells in the alveolar variant were identical to the

cells composing LCIS in a study by Nesland et al[57]. A spindle-cell trabecular pattern has also been described by Azzopardi consisting of trabeculae composed of short chains of elongated cells and bears a resemblance to sclerosing adenosis. This pattern was prominent in only 2 of 28 cases he reviewed[52]. The tubulolobular variant of I.L.C. was described by Fisher in 1977[58]. In this variant tubular differentiation is seen in otherwise characteristic I.L.C. This pattern was seen in 7 of 28 cases reviewed by Azzopardi, but was prominent in only 2. He describes the tubules as being of the "closed" or "almost closed" variety[52].

Some authors feel the signet-ring cell type of carcinoma to be another morphological variant of I.L.C.[53,54]. Focal signet-ring cell formation is not uncommon in I.L.C. and should be classified with I.L.C. of the classical variety[9]. Signet-ring cells have also been described in association with invasive duct carcinomas[55]. It is thought that there are two types of signet-ring cells of the breast. Harris[59] has described one in which mucin is produced and stored in the cisternae of the endoplastic reticuulum and is thought to be related to the signet-ring cells of duct carcinomas. Another type, described by Azzopardi[60] and thought to be associated with I.L.C., is the result of mucin accumulation in intracytoplasmic lumina which causes gross distension of these cells resulting in an appearance at the light microscope level indistinguishable from the type of signet-ring cells described by Harris.

The incidence of I.L.C. varies between 0.7[72] - 20%[73] (see table IV). There are geographical and racial variations in the incidence of this type of carcinoma. It has been shown that Negroes have a lesser incidence than Caucasians[61]. Japanese women have an incidence of I.L.C. about half that of North American women (3.5% vs. 7.2%)[30]. Problems in the classification of this tumour are probably the most important factor in the rather large variabilty in the reported

incidences of this tumour. In the opinion of Azzopardi, an incidence of at least 8% among invasive breast cancers should be seen, otherwise the histological criteria should be revised.

Associated LCIS with I.L.C. is reported in anywhere from 66[33] to 80[49,52] to 98%[31] of cases. This high association suggests that lesions not entirely typical of I.L.C. without accompanying LCIS should bring about reluctance to diagnose I.L.C.[49]. Wheeler and Enterline suggest that if coexisting LCIS is seen in less than 70% of cases of I.L.C., the diagnostic criteria for I.L.C. are questionable[49].

The age at diagnosis of I.L.C. varies from 48[31] to 53[49] to 58[32] years. It has not usually been found to be any different from that of invasive duct cancers. In Newman's series of 1966[31] 52 of 73 patients were premenopausal (71%) while 21 were menopausal or postmenopausal. In a more recent series from Dixon et al (1983)[32], only 36% of patients were premenopausal (37 of 103).

The prognosis of patients with I.L.C. has been reported as better[33,63], the same[49] and slightly worse[50,61] than those with invasive duct cancers. The prognosis has been shown to vary with the histological subtype of I.L.C. Dixon showed an improved prognosis with classic I.L.C. and with the alveolar variant while those classified as solid did not[33]. It must be pointed out however, that of those with classic I.L.C. or the alveolar variant, 62% were stage 1 and 20% were stage 2. This is not the usual situation seen with invasive duct cancers and it is not stated whether this factor was controlled for in the statistical analysis comparing I.L.C. with other invasive cancers. Fechner thought that the solid variant may have a better prognosis but emphasized that the sample size of his series was too small to make valid conclusions[51]. Fisher found what he identified as the tubulolobular variant to have a trend to a better prognosis, at least in the short term[58].

There is an increased incidence of bilaterality with this disease, ranging from less than 10 to 36%. Newman's original series in 1966 showed bilateral disease in 5 of 70 patients (7.1%)[31]. In a personal communication quoted by Enterline[49] from 1975, this incidence had risen to 36%. Dixon et al had an incidence of 20%[32] while Rosen and associates recorded an incidence of 28%[64]. Interestingly, Rosen also reported in the same study an incidence of bilaterality of 57% in those patients with invasive duct carcinoma with associated LCIS. Lewis and associates reviewed 52 patients with bilateral breast cancer. Of the 104 cases, lobular carcinoma was found in 36% (both *in situ* and invasive) again drawing attention to the propensity of this tumour to bilaterality[65]. Finally, Hislop has shown a risk factor of 4.3 for synchronous bilateral breast cancer in women with lobular carcinoma[66]. He did not show such a relationship with metachronous lesions.

Rosen's group[67] has shown the frequency of bilaterality to be related to multicentricity in the original tumour, patients with bilaterality having a higher frequency of multicentricity in the ipsilateral breast. As well, they demonstrated a higher incidence of bilaterality amongst those with estrogen positive tumours and in those with lower grade invasive duct tumours. Women with synchronous bilateral cancers had a higher mean age than those with no bilateral disease (58.5 vs. 53.5 years, $p < 0.001$). This relationship was also demonstated by Dixon et al[32]. No other epidemiological factors, including menstrual status, parity, family history, age at first birth, age at menarche, or prior oral contraceptive use have been *consistently* shown to increase the risk of bilateral disease. Hislop did show an increased risk of contralateral cancer 1 year after diagnosis of the first primary in those with a family history of breast cancer but did not show any relationship with multifocal tumours[66]. Burns et al found a significant association between the development of bilateral cancer and a later

age at the birth of the first child and a longer interval between menarche and that birth[68].

In 1975, Rosen et al demonstrated a higher frequency of estrogen receptor protein positivity in invasive lobular carcinoma[69]. A subsequent report by this group in 1981, with a larger series of patients, did not substantiate these early findings showing no difference in estrogen or progesterone receptor protein levels between those with invasive lobular carcinoma and those with invasive duct carcinoma[70]. Sifversward and co-workers found no difference in mean estrogen receptor concentrations between 25 cases of invasive lobular carcinoma and 218 cases of invasive duct cancer[71].

In summary, invasive lobular carcinoma has an incidence on average of approximately 10% of all invasive cancers. While the classic variety of I.L.C. remains the most common type, other "variant" forms are now being described. Associated LCIS is identified in 66-98% of cases. In some series I.L.C. has been more common in younger, premenopausal women while in more recent series, the age and menopausal status at the time of diagnosis has been comparable to that of invasive duct cancers. The prognosis has been shown to be both better, worse, and the same as I.D.C. and to vary with the histological subtype of the tumour. Bilaterality is an important consideration in this disease ranging from 10 to 36%. No consistent predictors of those at greater risk of developing bilateral cancer in those with I.L.C. have been identified. Estrogen and progesterone receptor levels and positivities do not appear to be any different from those found in I.D.C..

Methods and Results

Over 3,000 pathology reports of surgical breast pathology at the University of Alberta Hospital from the years 1955 to June 1985 inclusive were carefully examined. From this, 1,025 cases with all diagnoses *except* those clearly described as invasive duct cancers with and without in situ duct cancer and non-proliferative benign biopsies were reviewed histologically. The diagnoses prior to histological review are shown in fig. 1 From these, all cases of duct carcinoma *in situ* with and without microinvasion, lobular carcinoma *in situ* , invasive lobular carcinoma with and without associated LCIS, invasive lobular carcinoma associated with other invasive cancers (+/- LCIS) and lobular carcinoma *in situ* associated with other invasive cancers were identified for clinical follow-up. The results of reclassification of breast cancers are shown in fig. 2.

The identification of DCIS was made using accepted histological criteria[9]. A variety of histological types were identified including those with solid, cribriform, papillary and micro-papillary patterns, those with prominent central necrosis ("comedo-carcinoma") and other more subtle changes such as the "clinging" type of carcinoma as described by Azzopardi[9]. Microinvasion was defined as invasion of the surrounding stroma in direct continuity with the in situ lesion. Any separate island of invasive tumour, however small, was considered to be a frankly invasive tumour.

The identification of LCIS required total involvement of one or more lobules with closely-packed, lightly cohesive small to medium sized cells with clear to lightly staining cytoplasm. Some degree of distension of the lobule was usually, athough not invariably, present. Mitotic figures were rare to non-existent with

nuclei fairly large for the cell size. Pagetoid spread was not uncommonly found, but careful examination always revealed a focus of LCIS within a lobule.

The identification of cases with I.L.C. was made with stringent criteria. The diagnosis of I.L.C. without accompanying LCIS was made only in the presence of classic I.L.C. Lesions with any focus of I.D.C. with classic I.L.C. were classified as I.L.C. with associated I.D.C.

Following the identification of cases, clinical information and follow-up was obtained at the University of Alberta Hospital and the Cross Cancer Institute in Edmonton, Alberta. Actuarial survival was computer calculated from a program contained in the SPSS^X Users Guide (2nd Edition, McGraw Hill, Toronto 1986). Actuarial survival curves were compared using the Lee-Desu statistic through a computer program contained in the same manual. The results of histological review and clinical follow-up for duct carcinoma *in-situ*, lobular carcinoma *in-situ* and all invasive cancers will be presented separately.

Duct Carcinoma *In Situ*

The results of histological review with regard to DCIS are outlined in table V. A total of 76 cases were identified including 57 "pure" duct carcinomas *in situ*, 4 cases of combined duct carcinoma *in situ* with lobular carcinoma *in situ* and 15 cases of duct carcinoma *in situ* with microinvasion. This represented 4% of all breast cancers and 78% of all in situ cancers of the breast. 34 patients had axillary node dissections, only one of which (3%) was positive in a patient with DCIS with microinvasion.

Clinical information on patients is summarized in table VI. The average age at diagnosis was 57 years and 44% were premenopausal. 67% presented with a discrete mass while 25% had a nipple discharge and 16% had Paget's disease of the nipple. Treatment is outlined in table VII. The treatment

according to time period is shown in fig. 3. No patient since 1969 has had a radical mastectomy.

15 patients had breast conserving procedures, 4 of which were "unintentional" incisional biopsies initially diagnosed as benign but subsequently reclassified as DCIS on histological review. One of these 15 patients presented with metastatic adenocarcinoma (skeletal) and had an excisional biopsy of a suspicious breast mass. Extensive sectioning revealed an intraductal carcinoma without any evidence of invasion. An autopsy did not reveal any other primary adenocarcinoma.

11 patients had previous invasive cancer of the opposite breast and were excluded from further follow-up. 2 patients were lost to follow-up soon after primary treatment. One patient presenting with metastatic disease was excluded from further follow-up. This left 62 patients for follow-up, 14 having had procedures preserving ipsilateral breast tissue and 48 having had mastectomy. The mean follow-up was 10 years with a minimum of 1 year and a maximum of 27 years.

Invasive carcinoma subsequently developed in 9 of 62 patients (14.5%). 3 followed mastectomy (6%), 2 being contralateral and 1 developed in the ipsilateral breast as a local recurrence 6 months following a modified radical mastectomy. No invasive cancer was seen in the original specimen upon extensive sectioning. The two contralateral cancers were both invasive lobular carcinomas with associated LCIS. In those treated with conservative surgery, 6 (43%) developed invasive cancers, all of which were invasive duct cancers and all were ipsilateral. One patient eventually developed a contralateral tubular carcinoma of the breast 10 years after the development of an ipsilateral invasive duct cancer, for a total of 7 cancers in 14 women. The mean time to the development of invasive cancer was 70 months. There were no identifiable

clinical, epidemiological or pathological indicators of those at risk of developing subsequent invasive carcinomas (see table VIII) although a younger age at menarche did approach significance

18 of 74 patients had bilateral cancers (24%). The histological types are listed in table IX. 11 of these carcinomas predated the diagnosis of contralateral DCIS while 7 developed subsequent to the diagnosis of DCIS. 14 were invasive cancers and 4 were in situ lesions. The only clinical factor associated with a higher incidence of bilateral cancers was family history with 46% of patients with bilateral carcinomas having a sister or mother with breast cancer and 69% having a history of *any* female relative with breast cancer (mother, sister, daughter, cousin or aunt). Of 20 patients with DCIS and a family history of breast cancer, 9 (45%) had bilateral disease. Of those without bilateral breast cancer, 9% had a sister or mother with breast cancer and 24% any female relative (see table X). These figures were both significant at $p < 0.01$ (Chi-square with Yate's correction).

There were no significant differences in survival between those with purely in situ lesions and those with microinvasion (see figure 4). The one patient with positive axillary lymph nodes remains alive and disease free 130 months following initial diagnosis.

4 patients (6%) developed metastatic breast cancer. 2 following breast conserving procedures (1 incisional biopsy only and 1 segmental resection) with subsequent ipsilateral invasive carcinoma, 1 following modified radical mastectomy with subsequent ipsilateral invasive carcinoma and 1 following the development of a contralateral invasive lobular carcinoma.

No difference in actuarial survival could be seen comparing those with breast conserving procedures and those with mastectomy and between those with 1° radiotherapy and those without it. See figures 5 and 6.

Lobular Carcinoma *in Situ*

21 cases of LCIS were identified, an incidence of 1% of all breast cancers and 22% of all in situ cancers. The clinical characteristics of patients with LCIS with a statistical comparison with DCIS are shown in table XII. Patients with LCIS were younger (48 vs. 55 years, $p < 0.01$), and a higher (although statistically insignificant) proportion were premenopausal. Bilaterality was much higher in those with LCIS (57% vs 24%, $p < 0.001$). 11 of 15 patients presented with a mass(73%), while 3 out of 14 (21%) presented with a nipple discharge, in the remainder, the features of presentation were not noted. 90% of cases presented in the upper quadrants while 10% were centrally located. 67% were premenopausal, not significantly different than DCIS. 75% of patients gave a family history of breast cancer in a female relative (mother, sister, daughter, cousin or aunt), significantly higher than those with DCIS.

12 patients had bilateral carcinomas (57%). 7 were previous invasive carcinomas, 5 of which were available for histological review. 3 showed the features of invasive lobular carcinomas with LCIS and 2 were invasive duct carcinomas with associated LCIS. 1 patient had a synchronous invasive lobular carcinoma, 1 patient had synchronous, bilateral LCIS and subsequently developed an invasive lobular carcinoma, 2 patients subsequently developed contralateral invasive carcinomas and 1 developed a contralateral DCIS with associated LCIS (see table XI).

Of the 21 cases of LCIS, 7 had previous mastectomies for invasive cancers and 6 subsequently underwent a second mastectomy for LCIS and were thus eliminated from further follow-up. 1 patient had bilateral mastectomy and was excluded. One patient had a combined lesion of LCIS with DCIS treated with biopsy only. She subsequently developed invasive duct carcinoma

of the same breast and died of metastatic disease. This patient was also eliminated from further follow-up. This left 13 patients available for follow-up, 4 of whom had incisional biopsy, 1had an ipsilateral subcutaneous mastectomy, and 8 had ipsilateral mastectomy. Of 8 lymph node dissections, none had metastatic disease. 4 of 13 patients developed invasive cancers, while one other patient had a synchronous contralateral I.L.C. with associated LCIS. A sixth patient developed a DCIS in the opposite breast. Of the 4 patients developing subsequent invasive carcinomas, 2 were contralateral following simple mastectomy (1 "scirrhous" and 1 tubular with LCIS) and 2 were ipsilateral following biopsy (1 I.L.C. with LCIS and 1 I.D.C. with LCIS). The mean time to development of invasive cancer was 66 months ± 10.1 months with a minimum of 12 months and a maximum of 83 months. There were no clinical features identifying those at risk of developing invasive carcinoma, the major problem being the small number of cases involved (see table XIII). The actuarial survival is shown in Fig. 7 as compared with DCIS. No significant difference is demonstrated between these two types of in-situ carcinomas.

Invasive Lobular Carcinoma

136 cases of invasive lobular carcinoma (I.L.C.) were identified. This totalled 9% of all female breast cancers. 74 I.L.C. with associated LCIS, 48 cases of I.L.C. without associated LCIS and 14 cases of I.L.C. associated with invasive duct carcinoma (I.D.C.). As well, 19 cases of I.D.C with associated LCIS were also identified. All cases had a dominant pattern of "classic" I.L.C. The variant forms were infrequently identified and were never exclusive or dominant. 84 of the 136 cases of I.L.C. had associated LCIS (62%).

Clinical information and follow-up was obtained at the University of Alberta Hospital and at the Cross Cancer Institute in Edmonton, Alberta. A group of over 2000 patients with the histological diagnosis of invasive duct carcinoma

from 1971 to 1985 was accessed through computer files and compared with the data on this group of patients with I.L.C. This comparison group was felt to be acceptable since over 90% of the group can be assumed to have invasive duct carcinoma(even thought not histologically confirmed) because of known tumour frequencies. Anaplastic tumours including "inflammatory" carcinomas were not included in this group. Also excluded were medullary, mucinous , tubular, papillary, and comedo carcinomas. Information on bilaterality was not available through this method. However, information on bilaterality on patients at the W.W. Cross Cancer Institute was reviewed in an article by Burns et al[68] in 1984. Data from this review was used to compare the incidence of bilaterality between the overall population of patients with breast carcinoma and those with I.L.C.

In the overall group of 136 patients with I.L.C., the patients were significantly younger than those with invasive duct cancers (55 vs. 58 years). Patients with I.L.C. had a much higher incidence of bilaterality (21 vs. 5%) and a lower mean estrogen receptor protein level (47.4 vs. 66.4 *fm*/mg protein - see table XIV).

The stage at diagnosis was possible to determine in 110 patients. 31% were stage 1 (34 patients), 43% were stage 2 (47 patients), 22% were stage 3 (24 patients) and 4% were stage 4 (5 patients). Among 2,669 patients with invasive duct carcinoma, 27% were stage 1 (709 patients), 47% were stage 2 (1,264 patients), 20% were stage 3 (524 patients) and 6% were stage 4 (176 patients). There were no statistically significant differences between invasive lobular carcinoma and invasive duct carcinoma with respect to the stage at diagnosis.

After dividing the 136 patients into histological subgroups some further differences are seen. Those with I.L.C. and no associated LCIS showed little difference from those with invasive duct cancers (table XVI). There was still a

significantly higher incidence of bilaterality (14.9%), but not as marked as in other histological subgroups. In those patients with I.L.C. with associated LCIS (table XV), again there was a significantly lower age at diagnosis (53 yrs) as well as a higher percentage of premenopausal patients (48.6%). These patients demonstrated a high incidence of bilaterality (24.3%) and significantly lower estrogen and progesterone receptor protein levels when compared with those patients with I.D.C..

In those patients with invasive lobular carcinomas with areas of invasive duct car-cinoma (table XVII), again there was a significantly lower age at diagnosis (47 yrs). A higher incidence of bilaterality was demonstrated, but this was not statistically significant.

In a small group of 19 patients with invasive duct carcinoma with associated LCIS (table XVIII), a much younger age group (47.8 yrs) is seen with a high proportion of premenopausal patients (58 %). Both of these are of high statistical significance when compared with invasive duct carcinomas without associated LCIS. The incidence of bilaterality is also significantly increased in this group of patients when compared with invasive duct cancers (22% vs 5%).

131 patients with I.L.C. were eligible for follow-up with respect to bilaterality (of 136 patients, 3 patients were lost to follow-up soon after diagnosis and 2 patients died postoperatively following the diagnosis of the first primary, one from a pulmonary embolism and the second from radiation pneumonitis) . 26 patients developed bilateral disease. In 5 patients, the first primary was not of lobular origin, 2 being invasive duct carcinomas, 1 a medullary carcinoma and 2 cases of duct carcinoma *in situ* . All of these were reviewed histologically. In 3 patients with previous invasive breast cancers, the cases were not available for histological review. The first primary was diagnosed as "invasive carcinoma" in 2 cases and as "scirrhous" carcinoma in 1 case. In the remaining 18

cases, there were 12 cases of I.L.C. with associated LCIS, 3 cases of I.L.C. without LCIS, 2 cases of I.L.C. with associated I.D.C. and 1 case of I.L.C. with associated DCIS. 2 cases had synchronous bilateral breast cancers while the remainder had metachronous primaries in the opposite breast. The mean time to development of a second primary was 8.5 years (S.E. 1.7) with a minimum of 1 year and maximum of 40 years. The exact histological diagnoses of all bilateral carcinomas is detailed in table XXI. Those patients with bilateral carcinomas tended to have a lower age at diagnosis but not at a statistically significant level, the p value being just greater than 0.05. (52.6 vs 56.5 years. See table XX) As well, the size of the first primary was significantly larger in those developing second primaries than in those who did not (4.24 cm versus 3.23 cm).There were no other indicators of statistical significance identifying those at risk of developing bilateral breast cancer.

Treatment in 134 of 136 cases of I.L.C. could be determined and is outlined in table XXII. The treatment according to decade is shown in figure 8. No patient has had a radical mastectomy since October of 1969. At the present time, the most frequent mode of treatment is modified radical mastectomy.

Of the 136 cases of I.L.C., 6 were eliminated from further follow-up in the determination of survival because of a previous breast primary for which the pathology could not be reviewed (3 cases) or were invasive ductal carcinomas (3 cases). 3 cases were lost to follow-up soon after diagnosis and 2 patients died in the perioperative period leaving 125 cases for follow-up. The mean follow-up for these cases was 9 years with a minimum of 10 months and a maximum of 26 years. In the comparison of survival between I.L.C. and I.D.C., a survival advantage is seen for those patients with lobular carcinomas. This improved survival is seen both in those with I.L.C. without associated LCIS and in those with associated LCIS. (see fig. 9-11).

In those patients with I.L.C. with associated I.D.C., 13 patients were eligible for follow-up The mean period of follow-up was 86 months with a minimum of 12 and a maximum of 263 months. No survival advantage is seen in comparison with patients with I.D.C. (fig. 12), and the survival curves are virtually superimposable.

In those patients with I.D.C. with associated LCIS, 16 patients were eligible for follow-up. The mean period of follow-up was 85 months, with a minimum of 20 and a maximum of 313 months. No difference is seen in actuarial survival in comparison with patients with I.D.C (fig 13).

In the overall group of 125 patients with I.L.C. (including all histological subtypes) eligible for follow-up, the only factor which correlated with survival was lymph node status. The stage at diagnosis (with the exception of stage 4 patients), size of primary, menopausal status, decade of diagnosis, and method of surgical treatment (whether simple, modified radical, or radical mastectomy) did not show any correlation with survival (see figures 14-19).

Discussion and Conclusions

In situ carcinomas comprised 5% of all cancers of the female breast at the University of Alberta Hospital from 1955 to 1985. Of these, 78% were *in situ* duct and 22% were *in situ* lobular carcinoma. These results are in general agreement with reported figures.

In situ lesions usually presented as a mass (approximately 70%). Those with DCIS presented with Paget's disease of the nipple in 16% of cases. The disparity in age at diagnosis (48 years in LCIS and 57 years in DCIS) mirrors the pattern consistently reported in the literature. A higher proportion of females with LCIS were premenopausal (67% versus 44%) although this was not statistically significant. A family history of breast cancer was very high in those with LCIS with 75% of patients giving a history of having either a mother, sister, aunt ,or daughter with a breast cancer. Only 33% of patients with DCIS had such a history. ($p < 0.01$)

Bilaterality was high with both lesions, although considerably higher with LCIS. With DCIS, the incidence of bilaterality is generally reported in the area of 15%[20,23,29,39]. In this series, 24% of patients had bilateral disease, a figure considerably higher than previously reported. It is a figure more in keeping with the data reported by Wellings[18], where DCIS was shown to be very commonly multicentric and bilateral (over 60%). Bilaterality was seen in over half of patients with LCIS, and in 48% (10/21), these were invasive carcinomas. In those patients with DCIS developing bilateral disease, over 70% had a family history of breast cancer. This increased risk of bilateral disease may indicate a propensity of all of the breast tissue to neoplastic transformation in those so affected by a familial predispostion to breast cancer. There were too few

patients with LCIS to adequately assess any features associated with bilaterality.

Of 14 patients with DCIS who underwent conservative breast surgery, 6 developed subsequent invasive carcinomas ipsilateral to the original in situ carcinoma and all were invasive duct cancers. This again mirrors what most observers have noted. This is contrasted with 13 patients with LCIS where half of the subsequent invasive cancers were contralateral and at least half were of ductal histology. No clinical or histo-pathological factors identifying those at risk of developing invasive cancers could be seen in either of these two types of in situ carcinomas.

It would appear that in situ lesions of the breast reflect a generalized disturbance of the breast epithelium. It may be that, rather than being two distinct entities, in situ duct and in situ lobular carcinomas may be part of a continuum of proliferative non-invasive changes indicating breast tissue with a propensity for neoplastic transformation. Whether the histological changes are recognized as lobular or ductal proliferations may merely reflect which cell populations of the terminal ductal lobular unit are active in that particular patient, in that particular area of the breast (on biopsy) with that particular hormonal milieu. The question to be asked is why invasive cancers following the diagnosis of DCIS are so often ipsilateral and *not* bilateral. It is clear that not all epithelial proliferations identified as DCIS will inevitably progress to invasive lesions. It is not clear why lesions identified clinically as a mass and then histologically as DCIS have such a propensity to go on to invasive cancers (40%) while the remaining foci of in situ cancers remain quiescent.

The propensity for bilaterality seen with in situ lobular carcinomas is also witnessed in those patients with the invasive form of lobular carcinoma. This is especially so in those patients with histological evidence of associated LCIS

where 24% had bilateral disease. A large number of these contralateral tumours were invasive duct or in situ duct carcinomas (10/17). This again illustrates a widespread disruption of the epithelial elements of the breast tissue at the terminal ductal lobular unit. Whether the in situ or invasive cancer is observed to be lobular or ductal most likely depends on which element predominates at an early time in the history of the particular tumour. Those patients with larger primaries had a higher incidence of bilaterality. This may reflect an even more generalized, multicentric neoplastic potential in that particular patient. Of great interest were those patients with an otherwise regular pattern of invasive duct carcinoma with associated LCIS. In this series of patients, 22% had bilateral breast cancers. It would again appear that the histological identification of LCIS is a potent indicator of a generalized disruption of the breast epithelium.

Those patients with invasive cancers and associated LCIS demonstrated a lower age at diagnosis. In those patients with I.L.C. with associated LCIS lower mean levels of both estrogen and progesterone receptor levels were demonstrated. This feature may be intrinsic to the tumour type or it may be in keeping with a lower age at diagnosis and a larger proportion of premenopausal females. Those women with I.L.C. without associated LCIS did not show a younger age at diagnosis or any differences in hormone receptor levels when compared with I.D.C. which would suggest that the observed differences in hormone receptor levels are secondary to the age of the patients. It is interesting that the prognosis for invasive lobular carcinoma was better when compared with invasive duct cancers even with lower mean hormone receptor levels in the tumours. This is contrary to what is often reported, where tumours with lower hormone receptor levels display a poorer survival[74].

The survival of patients with I.L.C. was improved over that of I.D.C., with or without associated LCIS. It was found that those patients with combined lesions of I.L.C. with I.D.C. had a prognosis identical to that of I.D.C.. It would appear that the prognosis is determined by the component with the worst prognosis.

Stage at diagnosis was a poor predictor of eventual survival, except those with advanced stage 4 disease. The size of primary tumour did not appear to indicate those patients at risk of developing advanced disease. The lymph node status was the only factor of importance in the determination of survival.

The type of surgical treatment did not influence survival whether radical, modified radical, or "simple" mastectomy. While actuarial survival has not changed over the past 30 years, it can be seen that as more conservative surgical approaches have emerged, it has not adversely affected the survival of these patients.

In conclusion, this study and other recent findings have demonstrated *in situ* carcinomas of the breast to be a generalized field change in the epithelium over the entire chest wall rather than being limited to one breast. Not all in situ lesions progress to invasive cancers, indeed it would appear that the minority of such lesions do so. Duct carcinomas in situ which become *clinically* apparent do appear to have a high risk of invasive cancer, almost exclusively in the same breast as the originally diagnosed *in situ* lesion. With LCIS, both breasts carry equal risk of invasive cancer. The consequences of the development of invasive disease can be severe and necessitates very close follow-up.

Bilaterality is frequent in both in situ lesions, moreso in those with LCIS. A family history of breast cancer in a patient with DCIS is a strong indicator of possible bilaterality and should be considered in treatment and follow-up.

Invasive lobular carcinoma composes 9% of female breast cancers and carries a very significant risk of bilateral disease. The presence of LCIS

compounds this problem even when associated with other non-lobular invasive cancers. These considerations should be born in mind along with other factors when determining optimal surgical treatment. The presence of a large primary invasive lobular carcinoma does not indicate a hopeless situation as these tumours will have a similar prognosis to smaller tumours. A definite improvement in survival is seen in patients with invasive lobular carcinoma when compared with those patients with invasive duct cancers.

TABLE I: RISK OF INVASIVE CANCER FOLLOWING LCIS†

	Study year				
	Hutter and Foote,[27] 1969,(n=40)*	Andersen 1977[13] (n=44)	Haagensen et al[8] 1978(n=263)	Rosen et al[12] 1979(n=99)	Wheeler et al[14] 1974(n=32)
Mean follow-up(yrs.)	§	15	15	24	18
Subsequent invasive cancer					
Ipsilateral(%)	25	20	11	18	4
Contralateral(%)	10	9	9	14	9
Overall Risk(%)	35	25	17	31	13

* this series includes 6 patients who underwent radical mastectomy at the time of original biopsy. These are excluded from the data. § Mean follow-up was not stated.

† after Wolmark[29]

TABLE II METHODS PROPOSED IN THE TREATMENT OF LCIS

Authors	Ipsilateral	Contralateral
Andersen(1977)[13]	follow-up	follow-up
Rosen et al(1980)[12]	mastectomy & low axillary node dissection	biopsy
Wheeler(1974)[14]	follow-up	follow-up
Haagensen et al(1978)[8]	follow-up	follow-up
Curletti et al(1981)[15]	follow-up	follow-up
Fisher & Fisher(1977)[26]	segmental mastectomy & low axillary node dissection	follow-up
Powers et al(1984)[37]	follow-up	follow-up
Hutter(1984)[17]	mastectomy & low axillary node dissection	biopsy
Sunshine et al(1985)[16]	mastectomy & low axillary node dissection	same as ipsilateral
Leis(1971)[35]	mastectomy	mastectomy

TABLE III RISK OF INVASIVE CANCER FOLLOWING INTRADUCTAL CARCINOMA TREATED BY BIOPSY ONLY†

	Series, yr.		
	Farrow, 1970[44] (n=25)	Betsill et al, 1978[42] (n=15)	Page et al, 1982[41] (n=25)
Mean Follow-up, yr	-	22	15
Subsequent Invasive Cancer, %	20	53	28
Interval to subsequent Invasive cancer, yr.	1-8	10	6

† from Wolmark[29]

TABLE IV. SUMMARY OF SELECTED SERIES OF INVASIVE LOBULAR CARCINOMA

Series(yr.)	# of cases	Inc.* (%)	Age†	Premeno-pausal (%)	Bilateral (%)	Prognosis vs. I.D.C	LCIS (%)
Newman (1966)[31]	73	5.2	48.3	71.2	36Ω	N.A.	99
Azzopardi (1979)[52]	30	14.7	N.A.	N.A.	16.6	N.A.	N.A.
Dixon et al (1982)[32,33]	103	10.3	58	36	20	better	66
Mcdivitt et al N.A. (1968)[50]	125	8.7	N.A.	N.A.	N.A.	same	

Ω as quoted by Enterline (1975)[49]
* incidence as percentage of all invasive breast cancers
† age at diagnosis in years

TABLE V. RESULTS OF HISTOLOGICAL REVIEW FOR DCIS

INITIAL DIAGNOSIS (NUMBER OF CASES)	REVISED DIAGNOSIS (NUMBER OF CASES)
50 DCIS	38 DCIS 8 DCIS+ Microinvasion 4 Invasive Duct Ca
3 DCIS+ LCIS	3 DCIS+LCIS
10 DCIS+ Microinvasion	7 DCIS+ Microinvasion 3 Invasive Duct Ca
12 Paget's Disease of the nipple	12 DCIS+ Paget's Disease
195 Benign Lesions	3 DCIS 1 DCIS+ LCIS

4 other cases of DCIS were identified from the following cases: cyst-adenocarcinoma, LCIS, carcinoma N.O.S., and adenocarcinoma N.O.S.

TABLE VI.
CLINICAL DATA - DUCT CARCINOMA IN SITU

age at diagnosis	56.7± 1.72*
% premenopausal	44 (31/71)
age at menarche	13.4± 0.33
age at menopause	49.0± 1.23
parity	3.0 ± 0.27
age at first birth	25.8± 0.87
age at last birth	32.4± 0.38
% nulliparous	13 (8/63)
% breast fed	68 (38/56)
% with mass as initial symptom	67 (36/54)
% with nipple discharge	25 (14/55)
% with Paget's Disease	16 (14/76)
Location of tumour (%)	
upper outer quadrant	41 (20/49)
upper inner quadrant	6 (3/49)
lower outer quadrant	10 (5/49)
lower inner quadrant	2 (1/49)
central	39 (19/49)
size	1.9 ± 0.31

* mean ± S.E.M.

TABLE VII- METHOD OF TREATMENT - DCIS

Radical Mastectomy	4
Radical Mastectomy+Radiotherapy	5
Modified Radical Mastectomy	13
Modified Radical Mastectomy+Radiotherapy	0
Simple Mastectomy	29
Simple Mastectomy+Radiotherapy	7
Excisional Biopsy	6
Excisional Biopsy+Radiotherapy	2
Segmental Resection	4
Incisional Biopsy	3

TABLE VIII. COMPARISON OF PATIENTS WITH DCIS DEVELOPING SUBSEQUENT INVASIVE CARCINOMA WITH THOSE WHO DID NOT

CHARACTERISTIC	INVASIVE CA*	NO INVASIVE CA	SIGNIFICANCE§
Age at Diagnosis	56.7 yrs. (6.1)	55.7 yrs. (2.1)	$p > 0.40$
Age at Menarche	11.8 yrs. (0.5)	13.6 yrs. (0.4)	$p > 0.05$
Age at Menopause	49.5 yrs. (2.1)	48.5 yrs. (1.6)	$p > 0.375$
% Premenopausal	50.0 (4/8)	46.7 (21/45)	$p > 0.50$
Parity	2.6 (0.6)	2.9 (0.3)	$p > 0.375$
Breast fed children	100% (5/5)	68.4% (26/38)	$p > 0.50$
Age at first birth	27.3 yrs. (1.9)	26.9 (1.1)	$p > 0.40$
Age at last birth	30.7 yrs. (1.5)	32.7 yrs. (1.0)	$p > 0.10$
Family History of Breast Cancer			
Maternal	16.7% (1/6)	4.8% (2/42)	$p > 0.50$
Sister	28.6% (2/7)	7.3% (3/41)	$p > 0.10$
Other Female	0%	14.6%(6/41)	$p > 0.50$
Size of Primary	1.7 cm (0.62)	1.9 cm (0.36)	$p > 0.375$

* Ca = carcinoma

§ - continuous variables were analysed with student's T test. Discrete variable analysis with Chi-square test with Yate's correction.

TABLE IX. HISTOLOGICAL TYPES OF BILATERAL BREAST CANCERSIN PATIENTS WITH DCIS

DIAGNOSIS	NUMBER OF PATIENTS
DCIS	3
LCIS	1
Invasive Lobular Carcinoma	4
Invasive Duct Carcinoma	3
Tubular Carcinoma	2
Mucinous Carcinoma	1
Medullary Carcinoma	1
Invasive Papillary Carcinoma	1
Invasive Carcinoma (unspecified)*	2

* these cases were not available for histological review.

TABLE X. COMPARISON OF PATIENTS WITH DCIS DEVELOPING BILATERAL BREAST CARCINOMAS WITH THOSE WHO DID NOT.

CHARACTERISTIC	BILATERAL	NON-BILATERAL	SIGNIFICANCE§
Age at Diagnosis	55.2 yrs. (3.4)	57.0 yrs. (2.1)	$p > 0.10$
Age at Menarche	13.0 yrs. (0.8)	13.5 yrs. (0.4)	$p > 0.10$
Age at Menopause	49.4 yrs. (2.4)	48.5 yrs. (1.5)	$p > 0.10$
% Premenopausal	37.5 (6/16)	47.0 (25/53)	$p > 0.50$
Parity	3.1 (1.9)	3.0 (0.3)	$p > 0.40$
Breast fed children	62% (8/13)	71% (30/42)	$p > 0.50$
Age at first birth	23.8 yrs. (1.3)	26.1 (1.0)	$p > 0.10$
Age at last birth	31.8 yrs. (3.3)	32.2 yrs. (1.0)	$p > 0.40$
Family History of Breast Cancer			
Maternal	15% (2/13)	2% (1/46)	$p > 0.10$
Sister	31% (4/13)	6.5% (3/46)	$p > 0.05$
Other Female	25% (3/12)	15%(7/46)	$p > 0.50$
Mother or Sister	46% (6/13)	9% (4/46)	$p < 0.01$
Any Female Relative	69% (9/13)	24% (11/46)	$p < 0.01$
Size of Primary	1.8 cm (0.62)	1.8 cm (0.36)	$p > 0.50$

§ - continuous variables were analysed with student's T test. Discrete variable analysis with Chi-square test with Yate's correction.

TABLE XI BILATERAL CANCERS IN PATIENTS WITH LCIS-
HISTOLOGICAL TYPES

Histological Type: First Carcinoma	Histological Type: Subsequent Carcinoma
LCIS	LCIS*
"Scirrhous" Carcinoma	LCIS
I.D.C. + LCIS	LCIS
I.D.C. + LCIS	LCIS
I.L.C. + LCIS	LCIS
I.L.C. + LCIS	LCIS
LCIS	I.L.C. + LCIS*
I.L.C. + LCIS	LCIS
LCIS	I.D.C. + LCIS
Invasive Carcinoma	LCIS
LCIS	Tubular Carcinoma + LCIS
LCIS	LCIS + DCIS

TABLE XII. COMPARISON OF PATIENTS WITH LCIS WITH THOSE WITH DCIS

CHARACTERISTIC	LCIS	DCIS	SIGNIFICANCE§
Age at Diagnosis	48 yrs. (1.8)	57 yrs. (1.7)	$p < 0.01$
Age at Menarche	13 yrs. (0.3)	13 yrs. (0.3)	$p > 0.10$
Age at Menopause	50 yrs. (1.7)	49 yrs. (1.2)	$p > 0.10$
% Premenopausal	67 (14/21)	44 (31/71)	$p > 0.10$
Bilaterality	62%(13/21)	24%(18/74)	$p < 0.001$
Parity	2.8 (0.6)	3.0 (0.3)	$p > 0.10$
Breast fed children	41% (7/17)	68% (38/56)	$p > 0.05$
Age at first birth	24 yrs. (1.1)	26 (0.9)	$p > 0.10$
Age at last birth	33 yrs. (1.9)	32 yrs. (0.9)	$p > 0.375$
Family History of Breast Cancer			
Maternal	20% (4/20)	5% (3/60)	$p > 0.05$
Sister	15% (3/20)	12% (7/60)	$p > 0.50$
Other Female	40% (8/20)	17% (10/59)	$p > 0.05$
Any female relative	75% (15/20)	33% (20/60)	$p < 0.01$

* Ca = carcinoma

§ - continuous variables were analysed with student's T test. Discrete variable analysis with Chi-square test with Yate's correction.

TABLE XIII. COMPARISON OF PATIENTS WITH LCIS DEVELOPING SUBSEQUENT INVASIVE CARCINOMA WITH THOSE WHO DID NOT.

CHARACTERISTIC	INVASIVE CA*	NO INVASIVE CA	SIG.§
Age at Diagnosis	51.2 yrs. (4.8)	49.9 yrs. (2.5)	$p > 0.375$
Age at Menarche	12.8 yrs. (1.3)	12.9 yrs. (0.35)	$p > 0.40$
Age at Menopause	52.0 yrs. (0.58)	53.0 yrs. (1.2)	$p > 0.375$
% Premenopausal	80.0 (4/5)	75.0 (6/8)	$p > 0.50$
Parity	1.4 (0.87)	2.1 (0.58)	$p > 0.375$
Breast fed children	100% (5/5)	68.4% (26/38)	$p > 0.50$
Age at first birth	22.5 yrs. (2.5)	24.0 (0.89)	$p > 0.375$
Age at last birth	29.5 yrs. (0.5)	32.4 yrs. (3.7)	$p > 0.10$
Family History of Breast Cancer			
Maternal	25.0% (1/4)	14.3% (1/7)	$p > 0.50$
Sister	25.0% (1/4)	0% (0/7)	$p > 0.50$
Other Female	50%(2/4)	43%(3/7)	$p > 0.50$

* Ca = carcinoma

§ - continuous variables were analysed with student's T test. Discrete variable analysis with Chi-square test with Yate's correction.

TABLE XIV. CLINICAL DATA INVASIVE LOBULAR CARCINOMA COMPARED WITH INVASIVE DUCT CARCINOMA

	I.L.C.	I.D.C.	SIGNIFICANCE§
Age at Diagnosis (years)	55.1 (1.02)	58.1 (0.23)	$p < 0.01$
% Premenopausal	41.5 (54/130)	33.6 (1076/3201)	$p > 0.05$
Family History			
maternal	9.1 (10/111)	6.1 (192/3129)	$p > 0.10$
sister	10.3 (11/107)	8.9 (261/2928)	$p > 0.50$
other female*	21.2 (22/104)	27.0 (623/2300)	$p > 0.10$
% Positive Axillary Nodes at Presentation	42.1 (45/107)	45.4 (1106/2437)	$p > 0.05$
Bilaterality†	21.0 (26/124)	4.9 (106/2125)	$p < 0.001$
Mean Estrogen Receptor Level (fm / mg protein)	47.4 (7.59)	66.4 (3.5)	$p < 0.001$
Mean Progesterone Receptor Level (fm / mg protein)	319.0 (56.4)	108.8 (6.9)	$p > 0.50$

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
* includes daughter, aunt or female cousin
† compared with data from Burns et al[68]

TABLE XV. CLINICAL DATA ON INVASIVE LOBULAR CARCINOMA WITH ASSOCIATED LCIS COMPARED WITH INVASIVE DUCT CARCINOMA

	I.L.C.+LCIS	I.D.C.	SIGNIFICANCE§
Age at Diagnosis (years)	53 (1.41)	58.1 (0.23)	$p < 0.001$
% Premenopausal	48.6 (34/70)	33.6 (1076/3201)	$p < 0.02$
Family History			
maternal	9.7 (6/62)	6.1 (192/3129)	$p > 0.10$
sister	8.3 (5/60)	8.9 (261/2928)	$p > 0.50$
other female*	28.3 (13/59)	27.0 (623/2300)	$p > 0.50$
% Positive Axillary Nodes at Presentation	36.4 (20/55)	45.4 (1106/2437)	$p > 0.10$
Bilaterality†	26.6 (17/64)	4.9 (106/2125)	$p < 0.001$
Mean Estrogen Receptor Level (fm / mg protein)	21.0 (4.81)	66.4 (3.5)	$p < 0.001$
Mean Progesterone Receptor Level (fm / mg protein)	50.5 (20)	108.8 (6.9)	$p < 0.02$

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
* includes daughter, aunt or female cousin
† compared with data from Burns et al[68]

TABLE XVI. CLINICAL DATA INVASIVE LOBULAR CARCINOMA WITHOUT ASSOCIATED LCIS COMPARED WITH INVASIVE DUCT CARCINOMA

	I.L.C.	I.D.C.	SIGNIFICANCE§
Age at Diagnosis (years)	59.9 (1.51)°	58.1 (0.23)	$p > 0.10$
% Premenopausal	27.2 (12/44)	33.6 (1076/3201)	$p > 0.10$
Family History			
maternal	11.1 (4/36)	6.1 (192/3129)	$p > 0.10$
sister	9.1 (3/33)	8.9 (261/2928)	$p > 0.50$
other female*	15.2 (5/33)	27.0 (623/2300)	$p > 0.50$
% Positive Axillary Nodes at Presentation	48.7(19/39)	45.4 (1106/2437)	$p > 0.50$
Bilaterality†	15.2 (7/46)	4.9 (106/2125)	$p < 0.02$
Mean Estrogen Receptor Level (*f*m / mg protein)	63.7 (15.44)	66.4 (3.5)	$p > 0.10$
Mean Progesterone Receptor Level (*f*m / mg protein)	431.0 (10.4)	108.8 (6.9)	$p > 0.50$

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
° standard error of the mean
* includes daughter, aunt or female cousin
† compared with data from Burns et al[68]

TABLE XVII. CLINICAL DATA ON INVASIVE LOBULAR CARCINOMA WITH ASSOCIATED INVASIVE DUCT CARCINOMA COMPARED WITH INVASIVE DUCT CARCINOMA ALONE

	I.L.C.+I.D.C.	I.D.C.	SIGNIFICANCE§
Age at Diagnosis (years)	49.0 (1.51)°	58.1 (0.23)	$p < 0.001$
% Premenopausal	57.1 (8/14)	33.6 (1076/3201)	$p > 0.10$
Family History			
maternal	0 (0/11)	6.1 (192/3129)	$p > 0.50$
sister	20.0 (2/10)	8.9 (261/2928)	$p > 0.50$
other female*	40.0 (4/10)	27.0 (623/2300)	$p > 0.10$
% Positive Axillary Nodes at Presentation	54.5(6/11)	45.4 (1106/2437)	$p > 0.50$
Bilaterality†	16.7 (2/12)	4.9 (106/2125)	$p > 0.10$
Mean Estrogen Receptor Level (*f*m / mg protein)	insufficient data	66.4 (3.5)	-
Mean Progesterone Receptor Level (*f*m / mg protein)	insufficient data	108.8 (6.9)	-

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
° standard error of the mean
* includes daughter, aunt or female cousin
† compared with data from Burns et al[68]

TABLE XVIII. CLINICAL DATA ON INVASIVE DUCT CARCINOMA WITH ASSOCIATED LCIS COMPARED WITH INVASIVE DUCT CARCINOMA ALONE.

	I.D.C.+LCIS	I.D.C.	SIGNIFICANCE§
Age at Diagnosis (years)	47.8 (1.64)°	58.1 (0.23)	$p < 0.001$
% Premenopausal	77.8 (14/18)	33.6 (1076/3201)	$p < 0.001$
Family History			
maternal	16.7 (3/18)	6.1 (192/3129)	$p > 0.05$
sister	11.1 (3/18)	8.9 (261/2928)	$p > 0.50$
other female*	31.0 (5/16)	27.0 (623/2300)	$p > 0.50$
% Positive Axillary Nodes at Presentation	47.4(9/19)	45.4 (1106/2437)	$p > 0.50$
Bilaterality†	22.2 (8/18)	4.9 (106/2125)	$p < 0.01$
Mean Estrogen Receptor Level (fm / mg protein)	insufficient data	66.4 (3.5)	-
Mean Progesterone Receptor Level (fm / mg protein)	insufficient data	108.8 (6.9)	-

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
° standard error of the mean
* includes daughter, aunt or female cousin
† compared with data from Burns et al[68]

TABLE XIX. CLINICAL DATA ON INVASIVE LOBULAR CARCINOMA WITH ASSOCIATED LCIS COMPARED WITH INVASIVE LOBULAR CARCINOMA WITHOUT LCIS

	I.L.C.+LCIS	I.L.C.	SIGNIFICANCE§
Age at Diagnosis (years)	53 (1.41)	59.9 (1.51)	$p < 0.001$
% Premenopausal	48.6 (34/70)	27.2 (12/44)	$p < 0.05$
Family History			
maternal	9.7 (6/62)	11.1 (4/36)	$p > 0.50$
sister	8.3 (5/60)	9.1 (3/33)	$p > 0.50$
other female*	28.3 (13/59)	15.2 (5/33)	$p > 0.10$
% Positive Axillary Nodes at Presentation	36.4 (20/55)	48.7 (19/39)	$p > 0.10$
Bilaterality	26.6 (17/64)	15.2 (7/46)	$p > 0.10$
Mean Estrogen Receptor Level (*fm* / mg protein)	21.0 (4.81)	63.7(15.44)	$p < 0.025$
Mean Progesterone Receptor Level (*fm* / mg protein)	50.5 (20)	431.0 (10.4)	$p > 0.05$

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
* includes daughter, aunt or female cousin

Table XX. CLINICAL DATA ON INVASIVE LOBULAR CARCINOMA. PATIENTS WITH BILATERAL DISEASE COMPARED WITH THOSE WITH UNILATERAL DISEASE ONLY.

	BILATERAL	UNILATERAL	SIGNIFICANCE§
Age at Diagnosis (years)	52.6 (1.41)	56.5 (1.21)	$p > 0.05$
% Premenopausal	54.2 (13/24)	34.7 (33/95)	$p > 0.10$
Family History			
maternal	9.1 (2/22)	8.8 (7/80)	$p > 0.50$
sister	10.0 (2/20)	8.3 (7/77)	$p > 0.50$
other female*	21.1 (4/19)	19.7 (15/76)	$p > 0.50$
% Positive Axillary Nodes at Presentation	36.4 (8/22)	42.1 (32/76)	$p > 0.50$
Mean Estrogen Receptor Level (fm / mg protein)	19.0 (7.33)	37.8(9.36)	$p > 0.10$
Mean Progesterone Receptor Level (fm / mg protein)	51.2 (43.1)	124.0 (66.4)	$p > 0.10$
Tumour Size (cm)	4.24 (0.53)	3.23 (.22)	$p < 0.05$

§ continuous variable analysis -students T test
discrete variable analysis - Chi-square with Yates correction
* includes daughter, aunt or female cousin

TABLE XXI. BILATERAL CANCERS ASSOCIATED WITH INVASIVE LOBULAR CARCINOMA

First Primary	Second Primary	Years to Development
I.L.C.	I.L.C. + LCIS	8
I.L.C.	I.D.C. + DCIS	13
I.L.C.	I.D.C. + DCIS	1
I.L.C. + LCIS	I.D.C. + DCIS	2
I.L.C. + LCIS	LCIS	6
I.L.C. + LCIS	DCIS	1
I.L.C. + LCIS	LCIS	2
I.L.C. + LCIS	I.D.C.	4
I.L.C. + LCIS	LCIS	synchronous
I.L.C. + LCIS	I.D.C.	9
I.L.C. + LCIS	LCIS	2
I.L.C. + LCIS	I.D.C. + LCIS	1
I.L.C. + LCIS	DCIS	3
I.L.C. + LCIS	DCIS	5
I.L.C. + LCIS	LCIS	synchronous
I.L.C. + DCIS	I.L.C. + LCIS	6
I.L.C. + I.D.C.	DCIS	14
I.L.C. + I.D.C.	I.L.C. + LCIS	2
I.D.C.	I.L.C. + LCIS	9
I.D.C. + DCIS	I.L.C.	3
DCIS	I.L.C. + LCIS	14
DCIS	I.L.C. + LCIS + DCIS	12
Medullary Ca	I.L.C. + LCIS	14
Scirrhous Ca*	I.L.C.	16
Carcinoma*	I.L.C. + LCIS	16
Carcinoma*	I.L.C. + DCIS	40
	Total	203
	Mean	8.5 (S.E. 1.7)

* Histology was not available for review on these cases

TABLE XXII. THE TREATMENT OF INVASIVE LOBULAR CARCINOMA

Radical Mastectomy	4
Radical Mastectomy plus radiotherapy	39
Modified Radical Mastectomy	29
Modified Radical Mastectomy plus radiotherapy	12
Simple Mastectomy	26
Simple Mastectomy plus radiotherapy	15
Segmental Resection	4
Segmental Resection plus radiotherapy	2
Incisional Biopsy plus radiotherapy*	3

* these three patients presented with advanced disease, locally and with distant metastasis

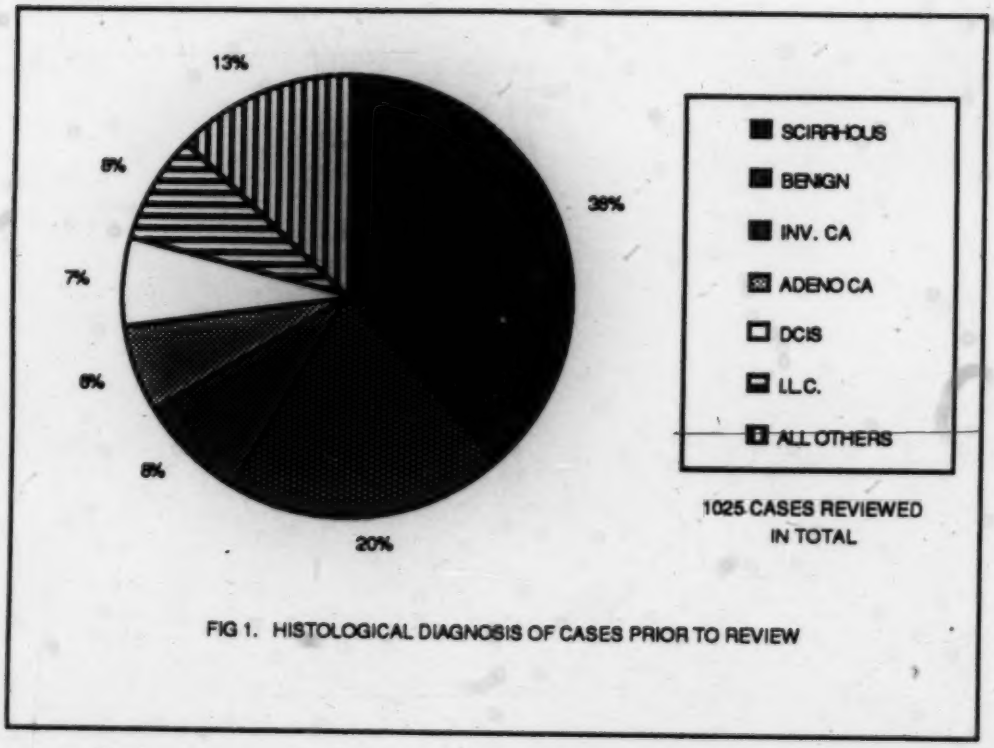


FIG 1. HISTOLOGICAL DIAGNOSIS OF CASES PRIOR TO REVIEW

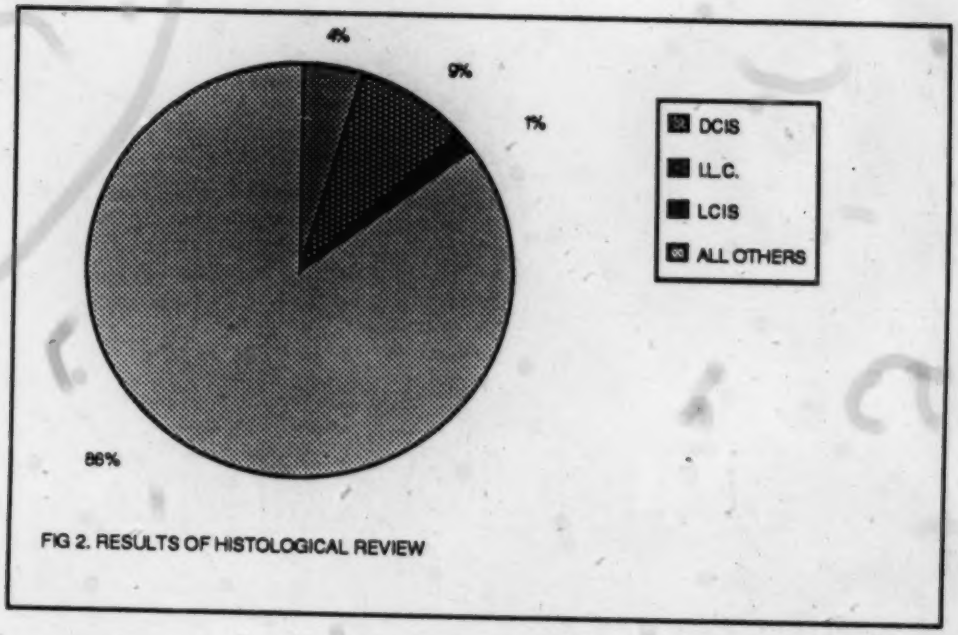


FIG 2. RESULTS OF HISTOLOGICAL REVIEW

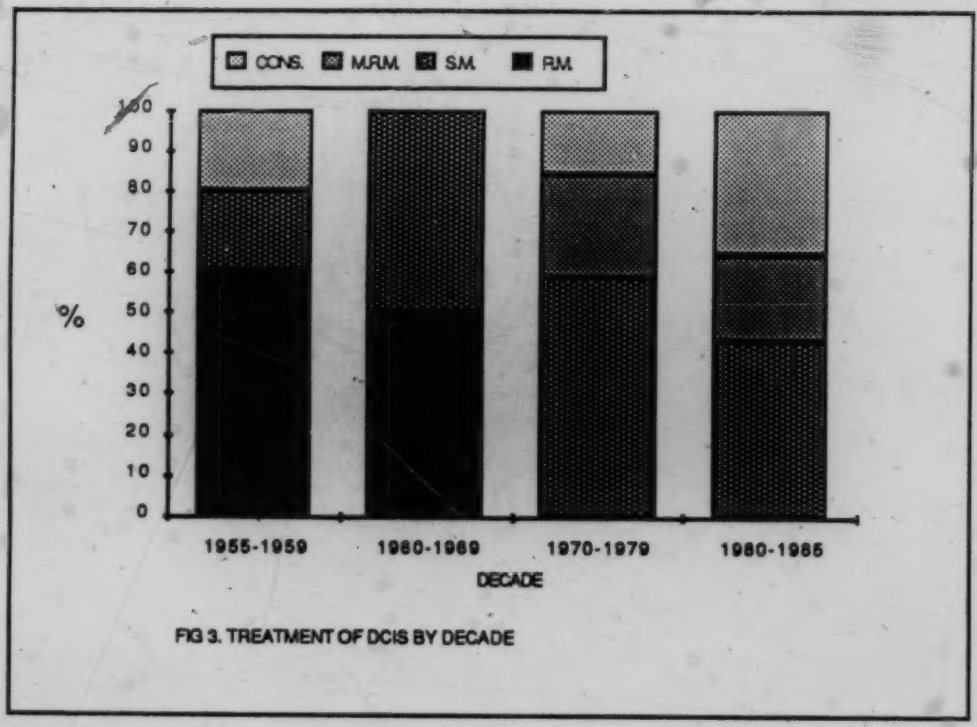


FIG 3. TREATMENT OF DCIS BY DECADE

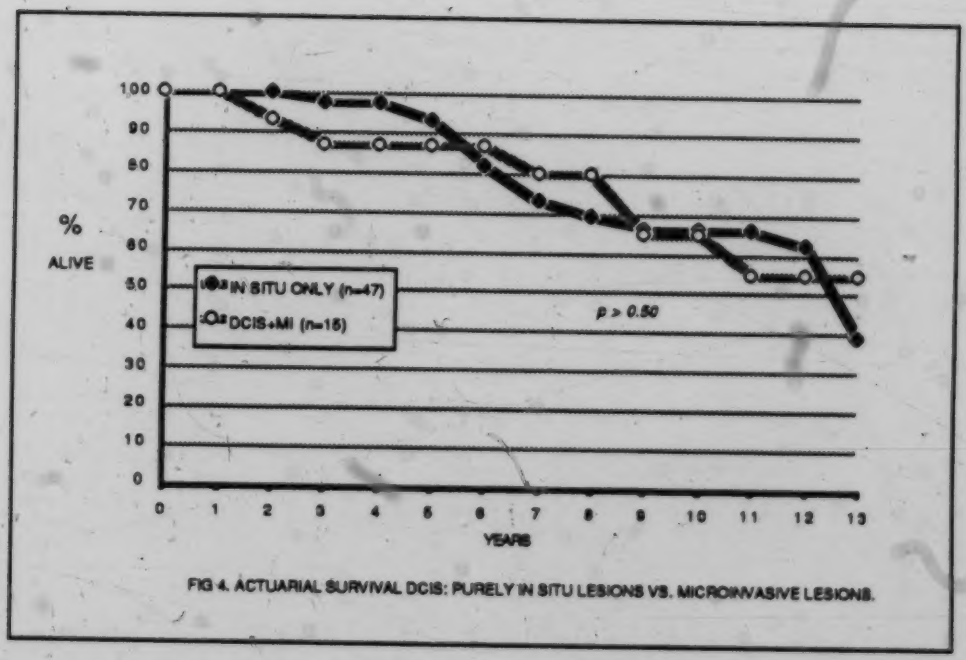


FIG 4. ACTUARIAL SURVIVAL DCIS: PURELY IN SITU LESIONS VS. MICROINVASIVE LESIONS.

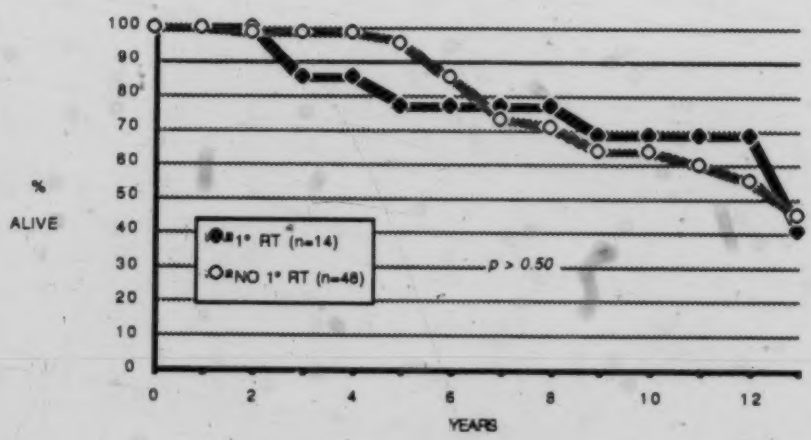


FIG 5. ACTUARIAL SURVIVAL: DCIS WITH PRIMARY RADIOTHERAPY (1°RT) VS. DCIS WITHOUT PRIMARY RADIOTHERAPY.

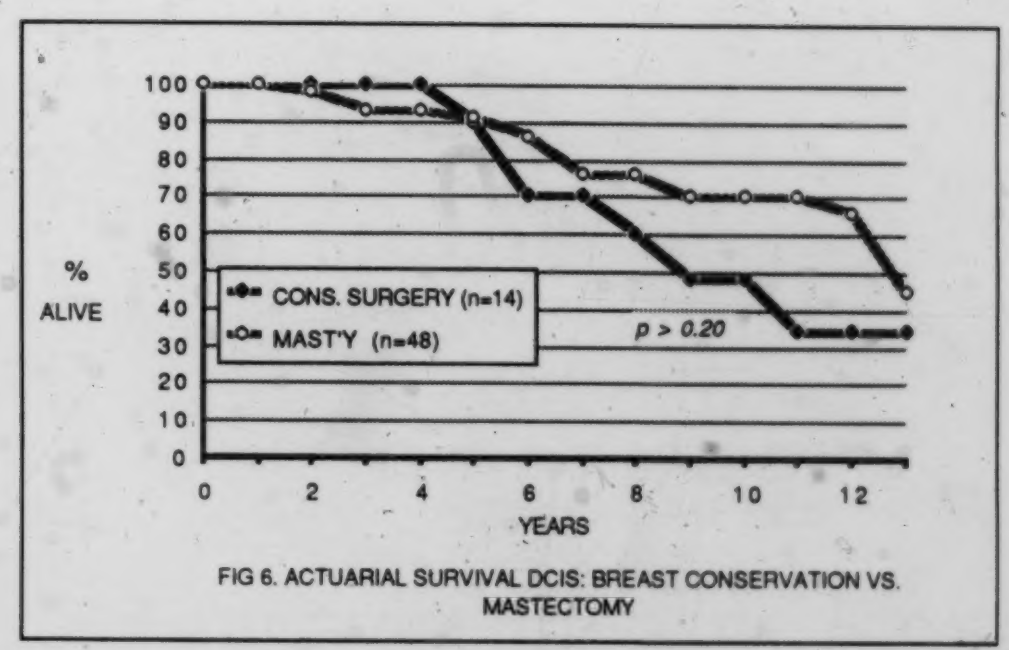


FIG 6. ACTUARIAL SURVIVAL DCIS: BREAST CONSERVATION VS. MASTECTOMY

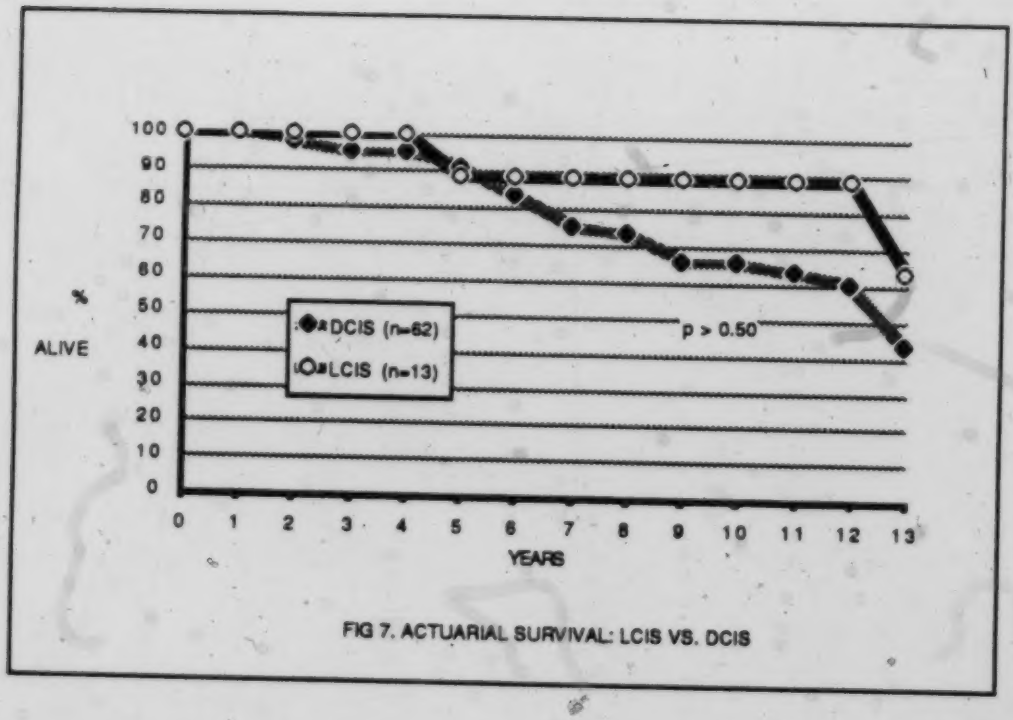


FIG 7. ACTUARIAL SURVIVAL: LCIS VS. DCIS

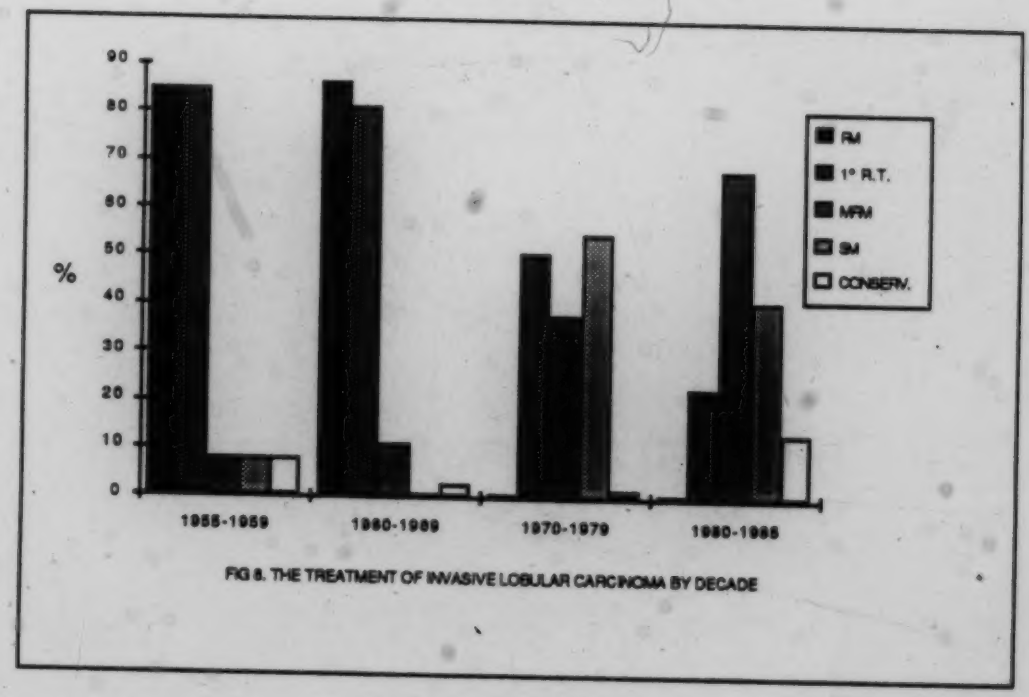


FIG 8. THE TREATMENT OF INVASIVE LOBULAR CARCINOMA BY DECADE

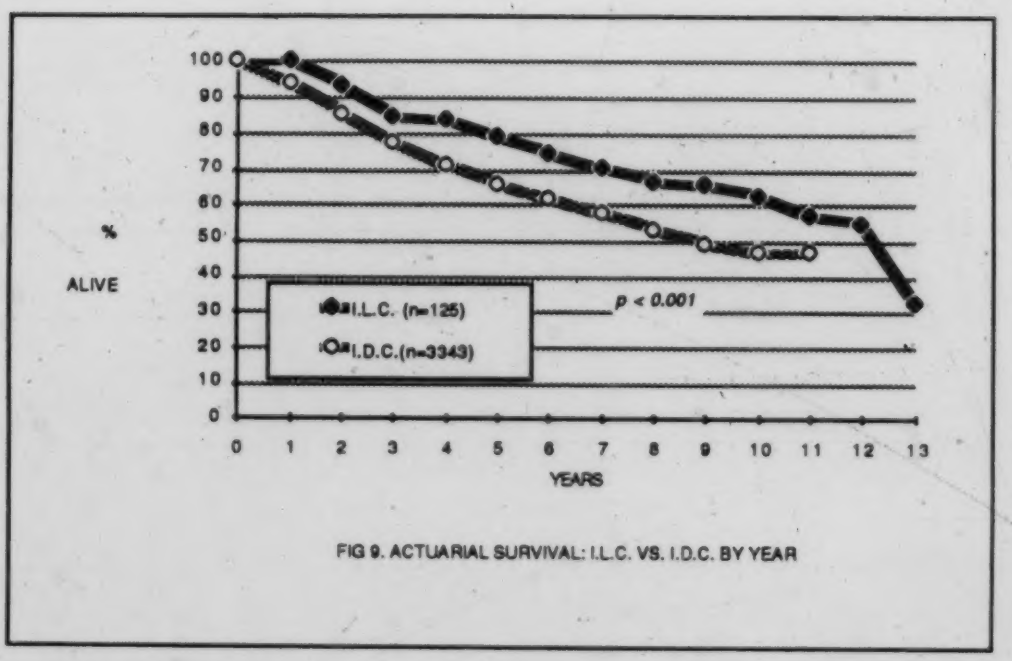


FIG 9. ACTUARIAL SURVIVAL: I.L.C. VS. I.D.C. BY YEAR

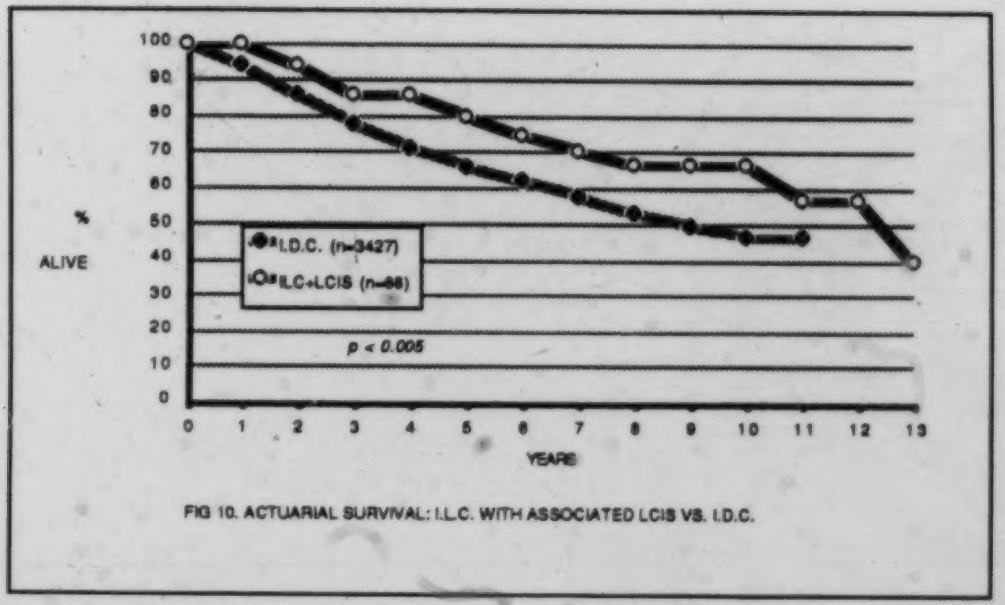


FIG 10. ACTUARIAL SURVIVAL: I.L.C. WITH ASSOCIATED LCIS VS. I.D.C.

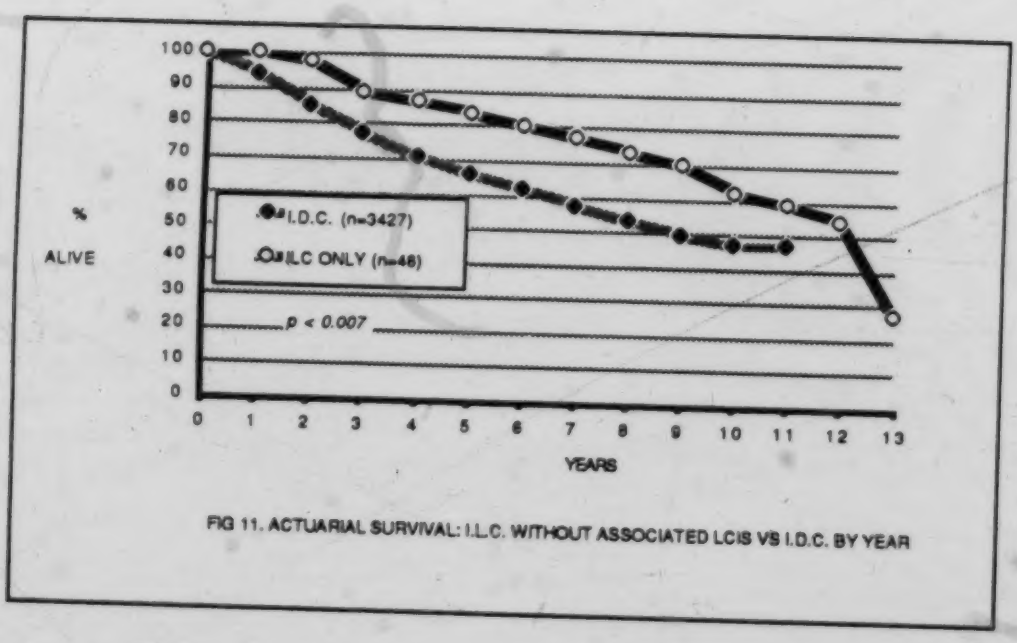


FIG 11. ACTUARIAL SURVIVAL: I.L.C. WITHOUT ASSOCIATED LCIS VS I.D.C. BY YEAR

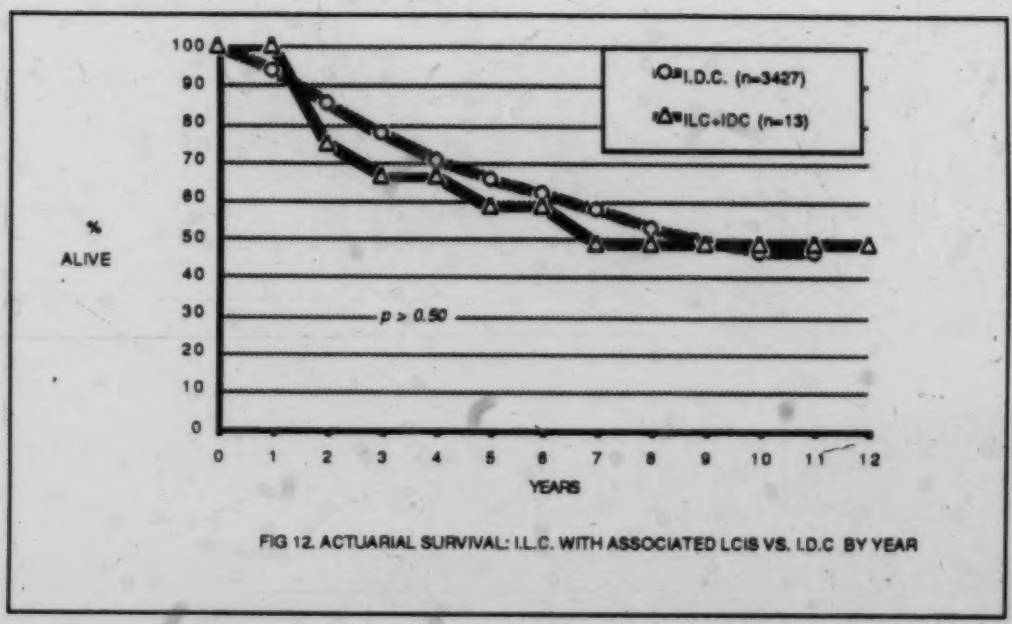


FIG 12. ACTUARIAL SURVIVAL: I.L.C. WITH ASSOCIATED LCIS VS. I.D.C BY YEAR

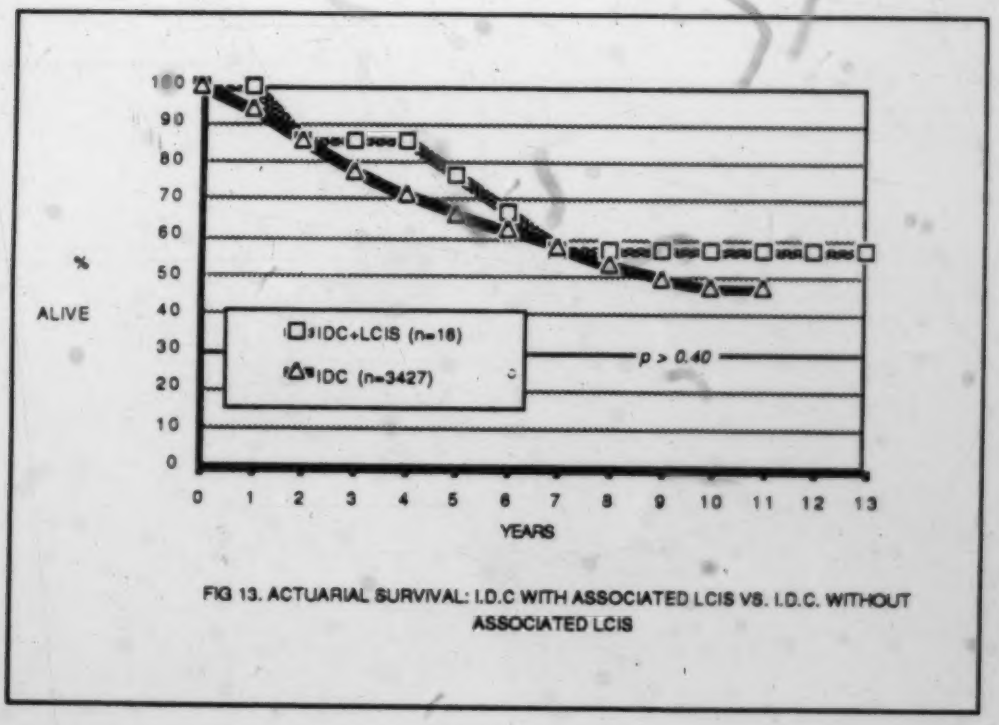


FIG 13. ACTUARIAL SURVIVAL: I.D.C WITH ASSOCIATED LCIS VS. I.D.C. WITHOUT ASSOCIATED LCIS

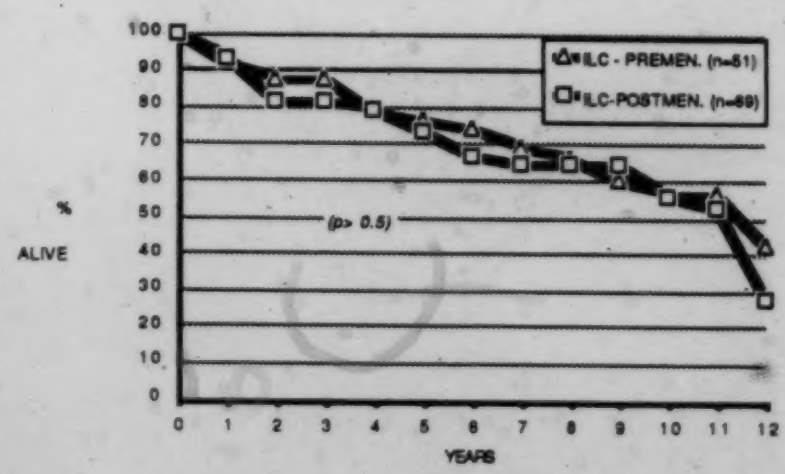


FIG 14. ACTUARIAL SURVIVAL: I.L.C PREMENOPAUSAL VS. POSTMENOPAUSAL

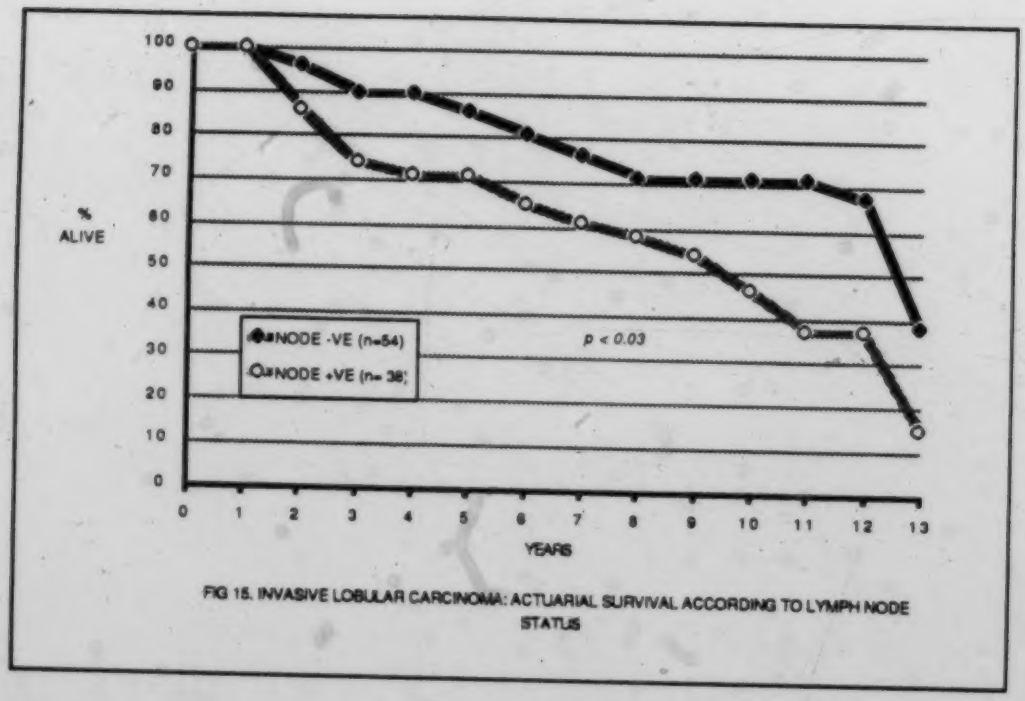


FIG 15. INVASIVE LOBULAR CARCINOMA: ACTUARIAL SURVIVAL ACCORDING TO LYMPH NODE STATUS

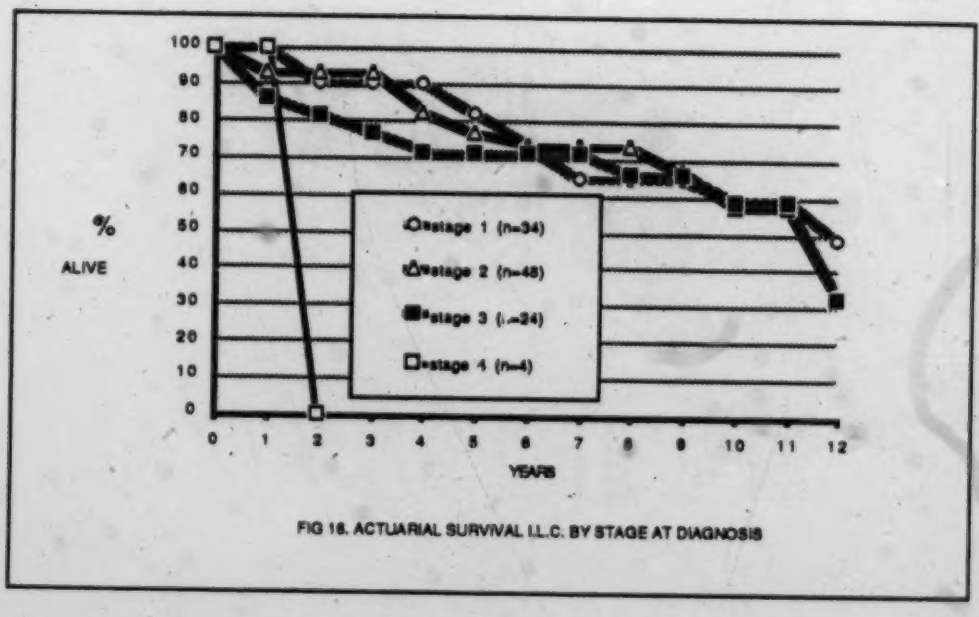


FIG 18. ACTUARIAL SURVIVAL I.L.C. BY STAGE AT DIAGNOSIS

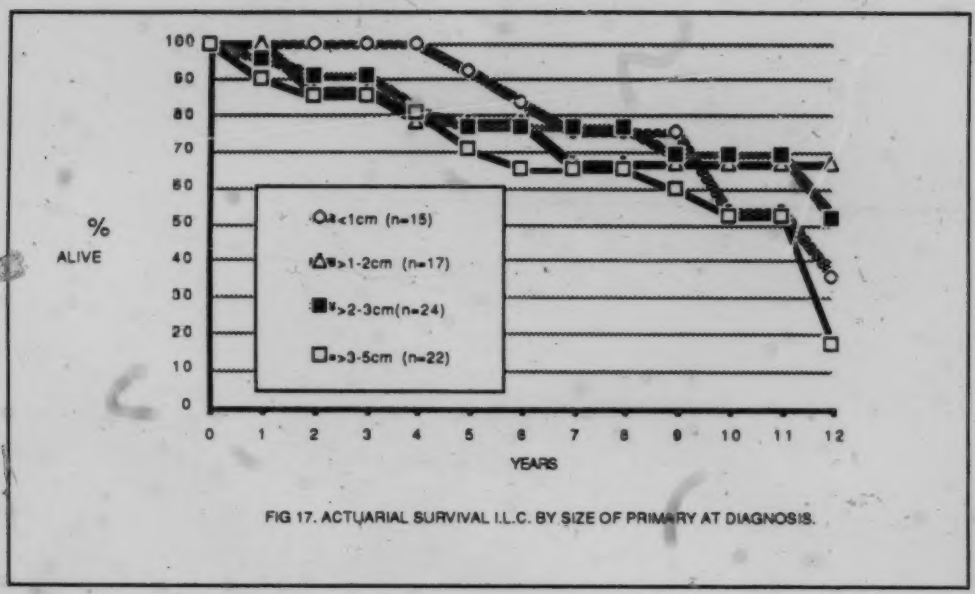


FIG 17. ACTUARIAL SURVIVAL I.L.C. BY SIZE OF PRIMARY AT DIAGNOSIS.

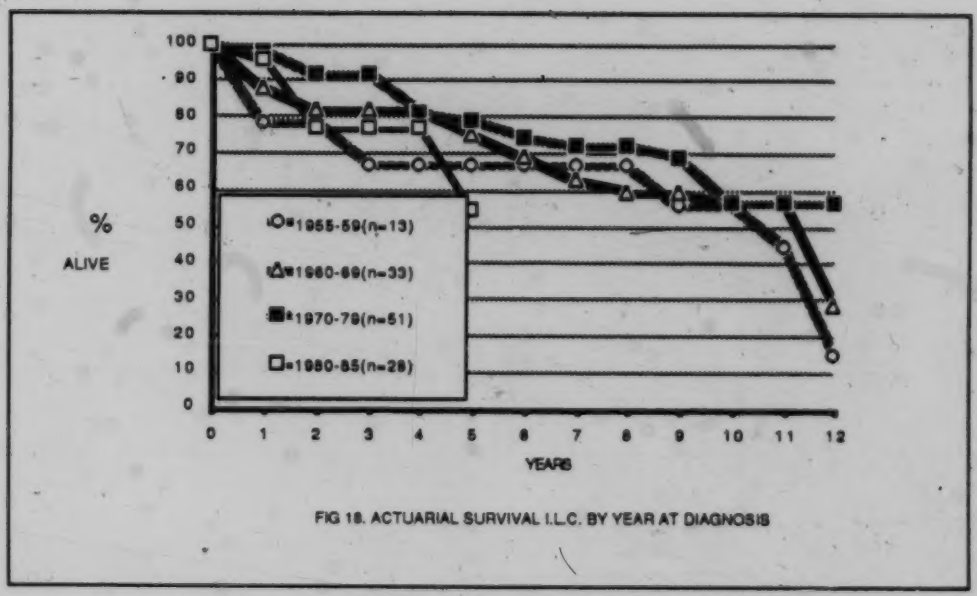


FIG 18. ACTUARIAL SURVIVAL I.L.C. BY YEAR AT DIAGNOSIS

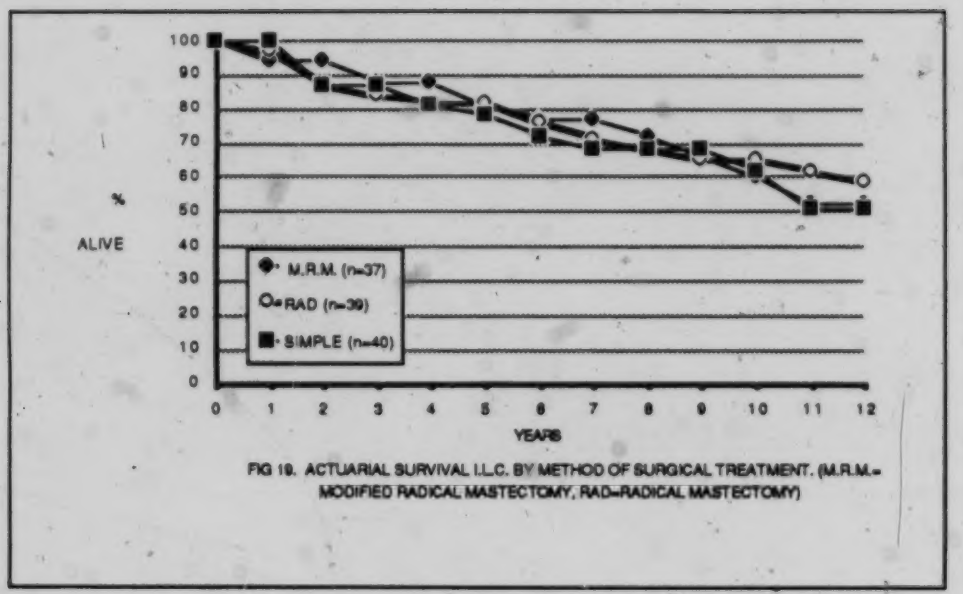


FIG 19. ACTUARIAL SURVIVAL L.L.C. BY METHOD OF SURGICAL TREATMENT. (M.R.M.= MODIFIED RADICAL MASTECTOMY, RAD=RADICAL MASTECTOMY)

References

1. Broders, A.C., Carcinoma *In Situ* Contrasted with Benign Penetrating Epithelium *J. Amer. Med. Ass.* 99: 1670-1674, 1932.

2. Smart, C.R., Myers, M.H., Gloeckler, L.A., Implications from SEER Data on Breast Cancer Management. *Cancer* 41:787-789, 1978.

3. Bedwani, R., Vana, J., Rosner, D., Schmitz, R.L., Murphy, G.P., Management and Survival of Female Patients with "Minimal" Breast Cancer: As Observed in the Long and Short Term Surveys of the American College of Surgeons. *Cancer* 47:2769-2778, 1981.

4. Rosner, D., Bedwani, R.N., Vana, J., Baker, H.W., Murphy, G.P., Noninvasive Breast Carcinoma. Results of a National Survey by the American College of Surgeons.*Ann. Surg.* 192: 139-147,1980.

5. Report of the Working Group to Review the National Cancer Institute-American Cancer Society Breast Cancer Detection Demonstration Projects. *JNCI* 62: 639-709, 1979.

6. Foote, F.W., Stewart, F.W., Lobular Carcinoma *in situ* : a Rare Form of Mammary Carcinoma. *Am. J. Pathol.* 17: 491-496, 1941.

7. Muir, R., Evolution of Carcinoma of Mamma. *J. Pathol. Bacteriol* 52: 155-172, 1941.

8. Haagensen, C.D., Lane, N., Lattes, R., Bodian, C., Lobular Neoplasia (so-called Lobular Carcinoma *in situ*) of the Breast. *Cancer* 42:737-769, 1978.

9. Azzopardi, J.G., Problems in Breast Pathology. Saunders, Philadelphia, 1979.

10. Rosen, P.P., Senie, R., Schottenfield, D., Ashikari, R. Noninvasive Breast Cancer- Frequency of Unsuspected Invasion and Implications for Treatment. *Ann. Surg.* 189: 377-382, 1979.

11. Rosen, P.P., Frozen Section Diagnosis of Breast Lesions. *Ann. Surg.* 187: 17, 1978.

12. Rosen, P.P., Lieberman, P.H., Braun, D.W., Kosloff, C., Adair, F., Lobular Carcinoma *In Situ* of the Breast. Detailed analysis of 99 patients with average follow-up of 24 years. *Am. J. Surg. Pathol.* 2: 225-251, 1978.

13. Andersen, J.A., Lobular Carcinoma *In Situ* of the Breast. An Approach to Rational Treatment.*Cancer* 39: 2597-2602, 1977.

14. Wheeler, J.E., Enterline, H.T., Roseman, J.M., Tomasulo, J.P., McILvaine, C.H., Fitts, W.T.,Kirshenbaum, J. Lobular Carcinoma *In Situ* of the Breast. Long Term Follow-up. *Cancer* 34:554-563, 1974.

15. Curletti, E., Giordano, J., *In Situ* Lobular Carcinoma of the Breast. *Arch. Surg.* 116:309-31, 1981.

16. Sunshine, J.A., Moseley, H.S., Fletcher, W.S., Krippaehne, W.W., Breast Carcinoma *in situ.* A Retrospective Review of 112 Cases With a Minimum 10 Year Follow-up. *Am. J. Surg.* 150: 44-51, 1985.

17. Hutter, R.V.P. The Management of Patients with Lobular Carcinoma *In Situ* of the Breast. *Cancer* 53: 798-802, 1984.

18. Alpers, C.E., Wellings, S.R., The Prevalence of Carcinoma *In Situ* in Normal and Cancer-Associated Breasts. *Hum. Pathol.* 16: 796-807, 1985.

19. Rosen, P.P. Lobular Carcinoma *In Situ* : Recent Clinicopathological Studies at Memorial Hospital *Path. Res. Pract.* 166: 430-455, 1980.

20. Urban, J.A., Papachristou, D., Taylor, J., Bilateral Breast Cancer. Biopsy of the Opposite Breast.*Cancer* 40:1968-1973, 1977.

21. Rosen, P.P., Braun, D.W., Lyngholm, B., Urban, J.A., Kinne, D.W. Lobular Carcinoma *In Situ* of the Breast: Preliminary Results of Treatment by Ipsilateral Mastectomy and Contralateral Biopsy. *Cancer* 47: 813-819, 1981.

22. Lambird, P.A., Shelley, W.M., The Spatial Distribution of Lobular *in situ* Mammary Carcinoma.Implications for Size and Site of Biopsy. *JAMA* 210: 689-693, 1969.

23. Ashikari, R., Huvos, A.G., Snyder, R. Prospective Study of Noninfiltrating Carcinoma of the Breast. *Cancer* 39: 435-439, 1977.

24. Ashikari, R., Huvos, A.G., Snyder, R.E., Lucas, J.C., Hutter, R.V.P., McDivitt, R.W., Schottenfeld,D. A Clinicopathological Study of Atypical Lesions of the Breast.*Cancer* 33: 310-317, 1974.

25. Hutter, R.V.P., Snyder, R., Lucas, J.C., Foote, F.W., Farrow, J.H. Clinical and Pathological Correlation with Mammographic Findings in LCIS. *Cancer* 23: 826- 839, 1969.

26. Fisher, E.R., Fisher, B., Lobular Carcinoma of the Breast: An Overview. *Ann. Surg.* 185:377-385, 1977.

27. Hutter, R.V.P., Foote, F.W. Lobular Carcinoma *In Situ.* Long Term Follow-up. *Cancer* 24: 1081-1085, 1969.

28. Lattes, R., Lobular Neoplasia (LCIS) of the Breast- an Histological Entity of Controversial Clinical Significance. *Path. Res. Pract.* 166: 415-429, 1980.

29. Wolmark, N., Minimal Breast Cancer: Advance or Anachronism? *Can. J. Surg.* 28: 252-55, 1985.

30. Rosen, P.P., Ashikari, R., Thaler, H., Ishikawa, S., Hirota, T., Abe, O., Yamamoto, H., Beattie, E.J.,Urban, J. A., Mike´, V., A Comparative Study of some Pathological Features of Mammary Carcinoma in Tokyo, Japan and New York, USA. *Cancer* 39: 429-434, 1977.

31. Newman, W. Lobular Carcinoma of the Female Breast. Report of 73 Cases. *Ann. Surg.* 164: 305-314, 1966.

32. Dixon, J.M., Anderson, T.J., Page, D.L., Lee, D., Duffy, S.W., Stewart, H.J. Infiltrating Lobular Carcinoma of the Breast: An Evaluation of the Incidence and Consequence of Bilateral Disease.*Br. J. Surg.* 70: 513-516, 1983.

33. Dixon, J.M., Anderson, T.J., Page, D.L., Lee, D., Duffy, S.W. Infiltrating Lobular Carcinoma of the Breast. *Histopathology* 6: 149-161, 1982.

34. McDivitt, R.W., Hutter, R.V.P., Foote, F.W., et al *In Situ* Lobular Carcinoma, A Prospective Follow-up Study Indicating Cumulative Patient Risks. *JAMA* 201: 82, 1967.

35. Leis, H.P., Selective, Elective, Prophylactic Contralateral Mastectomy. *Cancer* 28: 956-961, 1971.

36. Urban, J.A., Biopsy of the Normal Breast in Treating Breast Cancer. *Surg. Clin. N.A.* 49: 291, 1969.

37. Powers, R.W., O'Brien, P.H., Kreutner, A.,Jr., Lobular Carcinoma in Situ. *J. Surg. Onc.* 13: 269-273, 1980.

38. Westbrook, K.C., Gallager, H.S., Intraductal Carcinoma of the Breast. A Comparative Study. *Am. J. Surg.* 130: 667-670, 1975.

39. von Reuden, D.G., Wilson, R.E., Intraductal Carcinoma of the Breast. *Surg. Gynecol. Obst.* 158: 105-111, 1984.

40. Rosen, P.P., Snyder, R.E., Urban, J.A., Robbins, G.F., Correlation of Suspicious Mammograms and X-Rays of Breast Biopsies during Surgery. *Cancer* 31: 656-659,1973.

41. Page, D.L., Dupont, W.D., Rogers, L.W., Landenberger, M., Intraductal Carcinoma of the Breast: Follow-up after Biopsy Only. *Cancer* 49: 751-758, 1982.

42. Betsill, W.L., Rosen, P.P., Lieberman, P.H., Robbins, G.F., Intraductal Carcinoma. Long-term Follow-up After Treatment by Biopsy Alone. *J.A.M.A.* 239: 1863-1867, 1978.

43. Schwartz, G.F., Patchesfsky, A.S., Feig, S.A., Shaber, G.S., Schwartz, A.B., Multicentricity of Non-Palpable Breast Cancer. *Cancer* 45: 2913-2916, 1980.

44. Farrow, J.H., Current Concepts in the Detection of the Earliest of the Early Breast Cancers.*Cancer* 25: 468-477, 1970.

45. Fisher, B., Bauer, M., Margolese, R., Poisson, R., Pilch, Y., Redmond, C., Fisher, E.,Wolmark, N.,Deutsch, M., Montague, E., Saffer, E., Wickerman, L., Lerner, H., Glass, A.,Shibata, H.,Deckers, P., Ketcham, A., Oishi, R., Russell, I., Five-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Segmental Mastectomy With or Without Radiation in the Treatment of Breast Cancer. *N. Eng. J. Med.* 312: 665-673, 1985.

46. Ackermann's Textbook of Surgical Pathology, Moseby (1980).

47. Foote, F.W., Stewart, F.W., A Histologic Classification of Carcinoma of the Breast. *Surgery* 19, 74-99, 1946.

48. Wellings. S.R., An Hypothesis of the Origin of Human Breast Cancer from the Terminal Ductal Lobular Unit. *Path. Res. Pract.* 166(4): 515-535,1980.

49. Wheeler, J.E., Enterline, H.T., Lobular Carcinoma of the Breast In Situ and Infiltrating . In *Pathology Annual* 11: 161-188 (1976).ed. S.C. Sommers. Appleton Century Crofts, New York.

50. McDivitt, R.W., Stewart, F.A., Berg, J.W., Tumours of the Breast. Atlas of Tumour Pathology, Second Series. Armed Forces Institute of Pathology, Washington D.C.(1968).

51. Fechner, R.E., Histologic Variants of Infiltrating Lobular Carcinoma. *Human Pathology* 6: 373-378 ,1975.

52. Martinez, V. Azzopardi,J.G., Invasive Lobular Carcinoma of the Breast: Incidence and Variants.*Histopathology* 3, 467-488, 1979.

53. Steinbrecher, J.S., Silverberg, S.G., Signet-ring cell carcinoma of the breast. The mucinous variant of infiltrating lobular carcinoma? *Cancer* 37: 828-840, 1976.

54. Merino, M.J., Livolsi, V.A., Signet Ring Carcinoma of the Female Breast: A Clinicopathologic Analysis of 24 Cases. *Cancer* 48: 1830-1837, 1981.

55. Hull, M.T., Seo, I.S., Battersby, J.S., Csicsko, J.F., Signet -ring Carcinoma of the Breast: A Clinico- pathologic Study of 24 Cases. *Am. J. Clin. Path.* 73: 31-35, 1980.

56. Cubilla, A.L., Woodruff, J.M., Primary Carcinoid Tumour of the Breast. A Report of 8 Patients. *Am. J. Surg. Path.* 4: 283-292, 1977.

57. Nesland, J.M., Holm, R., Johannessen, J.V., Ultrastructural and Immuno-histochemical Features of Lobular Carcinoma of the Breast. *J. Hum. Path.* 145: 39-52, 1985.

58. Fisher, E.R., Gregorio, R.M., Redmond,C., and Fisher, B., Tubulolobular Invasive Breast Cancer: A Variant of Lobular Invasive Cancer. *Human Pathology* 8: 679-683, 1977.

59. Harris, M., Vasudev, K.S., Anfield, C., Wells, S., Mucin-Producing Carcinomas of the breast- Ultrastructural Observations. *Histopathology* 2: 177-188, 1978.

60. Gad, A., Azzopardi, J.G., Lobular Carcinoma of the Breast: A Special Variant of Mucin-Secreting Carcinoma. *J. Clin. Path.* 28: 711-716, 1975.

61. Azzopardi,R., Huvos, A.G., Urban, J.A., Robbins, G.F., Infiltrating Lobular Carcinoma of the Breast. *Cancer* 31: 110-116, 1973.

62. Van Bogaert, L-J, Maldague, P., Infiltrating Lobular Carcinoma of the Female Breast. Deviations from the Usual Histopathological Appearance. *Cancer* 45: 979-984.

63. Haagensen, C.D., Diseases of the Breast. 2nd. Edition. W.B. Saunders, Philadelphia,1971.

64. Lesser, L., Rosen, P.P., Kinne, W.K., Multicentricity and Bilaterality in Invasive Breast Cancer. *Surgery* 91(2) : 234-240, 1982.

65. Lewis, T.R., Casey, J., Buerk, C.A., Cammack, K.V., Incidence of Lobular Carcinoma in Bilateral Breast Cancer. *Am. J. Surg.* 144: 635-638, 1982.

66. Hislop, T.G., Elswood, J.M., Coldman, A.J., Spinelli, J.J., Worth, A.J., Ellison, L.G., Second Primary Cancers of the Breast: Incidence and Risk Factors. *Br. J. Cancer* 49:79-85, 1984.

67. Lesser, M.L., Rosen, P.P., Kinne, D.W., Multicentricity and Bilaterality in Invasive Breast Cancer.*Surgery* 91(2): 234-240, 1982.

68. Burns, P.E., Dabbs, K., May, C., Lees, A.W., Birkett, L.R., Jenkins, H.J., Hanson, J., Bilateral Breast Cancer in Northern Alberta: Risk Factors and Survival Patterns.*Can. Med. Ass. J.* 130: 881-886, 1984.

69. Rosen, P.P., Menendez-Botet, C.J., Nisselbaum, J.S., Urban, J.A., Mike´, V.,Fracchia, A., Schwartz, M.K., Pathological Review of Breast Lesions Analyzed for Estrogen Receptor Protein. *Cancer Res.* 35: 3187-3194, 1975.

70. Lesser, M.L., Rosen, P.P., Senie, M.A., Duthie, K., Menedez-Botet, C., Schwartz, M.K.,Estrogen and Progesterone Receptors in Breast Carcinoma: Correlations with Epidemiology and Pathology. *Cancer* 48: 299-309, 1981.

71. Silfversward,C., Gustafsson, J., Gustafsson, S.A., Humla, S., Nordenskjold, B., Wallgren, A.,Wrange, O., Estrogen Receptor Concentration in 269 Cases of Histologically Classified Human Breast Cancers. *Cancer* 45:2001-2005, 1980.

72. Donegan, W.L., Perez-Mesa, C.M., Lobular Carcinoma- an indication for elective biopsy of the second breast. *Annals of Surgery* 176: 178-187, 1972.

73. Fisher, E.R., Taylor, M., Changing pattern of some pathologic parameters of mammary carcinoma. *Cancer* 32: 130-1384, 1973.

74. Hubay, C.A., Arafah, B., Gordon, N.A., Guyton, S.P., Crowe, J.P., Hormone Receptors An Update and Application. *The Surgical Clinics of North America* 64:1155-1172, 1986.